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Usefulness of red cell distribution width as a predictor of amputation after embolectomy in acute lower limb ischemia

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ABSTRACT

Objectives: This study aimed to determine whether red cell distribution width (RDW) is an independent predictor of adverse outcomes in patients who underwent surgical embolectomy for acute lower limb ischemia.

Patients and methods: This retrospective study included 245 patients who underwent surgical embolectomy for acute lower limb ischemia between January 2008 and June 2012. Patients who had thrombosis of the atherosclerotic lesion and iliac or femoral stent thrombosis were excluded. The patients were divided into two groups according to the need for limb amputation after the initial embolectomy: 42 were in the limb amputation group (33 males, 9 females; mean age: 67.2±9.1 years; range, 52 to 85 years), and 203 were in the limb salvage group (132 males, 71 females; mean age: 58.4±9.3 years; range, 44 to 71 years). A multinomial logistic regression analysis was applied to determine the independent predictive effect of RDW and other parameters on major/minor amputation. The analysis was multivariately adjusted for age and sex to eliminate the confounding effect of other variables.

Results: Age (odds ratio [OR]=1.131, 95% confidence interval [CI]: 1.074-1.191, p<0.001), recurrent embolism in the same limb (OR=2.898, 95% CI: 1.238-6.780, p=0.01), urea level (OR=1.037, 95% CI: 1.013-1.062, p=0.003), and RDW (OR=1.324, 95% CI: 1.006-1.741, p=0.04) were significantly associated with the risk of major amputation in unadjusted multinominal logistic regression analysis, whereas the association of RDW with the risk of major amputation did not remain when adjusted for age and sex (OR=1.191, 95% CI: 0.963-1.474, p=0.10).

Conclusion: In conclusion, RDW may have a role in predicting adverse outcomes in patients treated for acute lower limb ischemia. However, it cannot be used as a stand-alone predictive marker.

Keywords: Acute lower limb ischemia, cardiovascular disease, peripheral artery disease, red cell distribution width.

Acute lower limb ischemia is a vascular emergency that occurs due to the sudden blockage of arterial blood perfusion to the limb and threatens limb viability. Despite advances in the management of cardiovascular diseases, the incidence of acute limb ischemia is still as high as 12 per 100,000 person-years due to the aging population. In addition, patients are at high risk of amputation and mortality, even if early revascularization is undertaken.[1,2] As an entity different from critical limb-threatening ischemia, which is characterized by collateral formation,[3] acute limb ischemia leads to rapid deterioration of the tissue metabolism. Uncompensated abrupt cessation of blood flow in the limb leads to ischemic inflammatory changes in all active tissues, such as skin, muscles, and nerves, which can progress to the gangrene of the limb if untreated.[4] Sudden occlusion of in-line arterial blood flow in the lower limb may be the result of an embolism from a remote source containing a thrombus (e.g., heart, abdominal aorta, or iliac arteries), or may result from the progression of a complicated atheroma plaque within the artery.[5] Although novel endovascular methods, such as percutaneous thrombolysis, thromboaspiration, and mechanical thrombectomy, have increasingly become applicable for complete or partial resolution of the occlusion over the last two decades, surgical embolectomy by a Fogarty balloon catheter remains an effective technique in the treatment of acute limb ischemia.[6]

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Amputation is the most dreadful complication after revascularization in patients presenting with acute lower limb ischemia. Although the time from arterial embolization to revascularization is of utmost vital importance,[7,8] it has been reported that a high score of ischemia, distal (below the knee) involvement, advanced age, the female sex, and anemia also predict amputation in acute lower limb ischemia.[1,9] Red cell distribution width (RDW), a laboratory indicator of anisocytosis, has recently been investigated for adverse outcomes in many clinical settings, and several studies have linked high RDW levels to high morbidity and mortality rates in atherosclerotic cardiovascular disease.[10,11] Although almost all of the studies have limitations that cannot definitively reveal a cut-off value of RDW to predict adverse outcomes, enough information has been provided to consider that RDW may be an additional laboratory marker during critical leg ischemia.[12,13] However, the relationship of RDW with limb salvage after acute lower limb ischemia has not been investigated yet. Since evidence has been provided that RDW is a risk factor for cardiovascular events, its diagnostic performance has been widely evaluated. Therefore, this study aimed to determine whether RDW is an independent predictor of adverse outcomes in patients who underwent surgical embolectomy for acute lower limb ischemia.

PATIENTS AND METHODS

This retrospective study was performed in the cardiovascular surgery department of a tertiary care hospital, and the study cohort was made up of 245 patients who underwent lower extremity embolectomy surgery between January 2008 and June 2012. Patients who had symptoms of acute critical limb ischemia, including new or worsening claudication or rest pain in the limb, paresthesia, paralysis, muscle weakness, or coldness in the extremity that continued for <7 days after the onset, and who underwent lower limb embolectomy surgery with the diagnosis of occlusive embolism were included in the study. Patients with acute lower limb ischemia symptoms due to thrombosis of the atherosclerotic lesion and patients with iliac or femoral stent thrombosis were excluded from the study. The patients were divided into two groups according to the need for limb amputation after the initial embolectomy: 42 were in the limb amputation group (33 males, 9 females; mean age: 67.2±9.1 years; range, 52 to 85 years), and 203 were in the limb salvage group (132 males, 71 females; mean age: 58.4±9.3 years; range, 44 to 71 years).

Preoperative diagnosis was made with ischemic findings in vascular physical examination and loss of normal triphasic arterial flow sound in femoral, popliteal, and below-the-knee pulses in the relevant extremity in portable Doppler ultrasound examination. The diagnosis of acute/subacute occlusive embolism, the location of the occlusive embolism, and the probable duration of the lesion were confirmed by color Doppler ultrasound. Digital subtraction angiography was performed in patients with suspected acute/subacute occlusion based on chronic peripheral arterial atherosclerotic disease (n=36, 15%). Demographic, clinical, and laboratory data of the patients were obtained by searching the archive records and the hospital's digital database and were recorded in the computer environment. Laboratory data included in the analysis were the results of total blood count and biochemistry sampled for preoperative preparation immediately after the decision for surgery was made. Red blood cell, RDW, and white blood cell parameters were routinely determined using a Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). The reference range of RDW at our hospital was %11.5-14.5.

Standard embolectomy procedure was performed in all patients using the appropriate diameters of Fogarty catheters (Edwards Lifesciences Corp., Irvine, CA, USA) with femoral artery or popliteal artery exploration according to the location of the embolism. The patients whose distal arterial flow was restored after the surgery and who had an improvement in the symptoms of critical leg ischemia were discharged to be followed up as outpatients. Reembolectomy was performed in patients whose distal perfusion was restored after embolectomy but then ceased again. In patients whose occlusive embolism did not improve despite the removal of the occlusive embolism, advanced angiographic examination was performed, and revascularization with a bypass graft was planned. Patients with worsening symptoms of critical limb ischemia and developing necrosis and gangrene after surgery were immediately scheduled for amputation. The level of amputation was jointly determined by vascular surgeons and orthopedic surgeons, and a balanced decision was made between healing the amputation stump without necrosis and leaving as much functional limb as possible. Major lower limb amputation was defined as amputation from any level above the ankle, and minor lower limb amputation was defined as heel, metatarsal, or digital amputation below the ankle level. Follow-up data were obtained from rehospitalization archive files and outpatient visit records.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were presented as number (%). Normal distribution of the continuous parameters was tested using visual histograms and the Kolmogorov-Smirnov test or the Shapiro-Wilk test. To compare the continuous parameters between the two groups (limb amputation and salvage), the independent samples t-test was used if there was a normal distribution, and the Mann-Whitney U test was used if the distribution was nonnormal. For categorical variables, Fisher exact test was used when one or more cells in the contingency table had counts of less than five. A chi-squared test was used for other categorical variables. Since the amputation as the outcome variable is two-leveled (major and minor amputation), a univariate multinomial logistic regression analysis was applied to determine the independent predictive effect of RDW and other parameters on the outcome. The analysis was multivariately adjusted for age and sex to eliminate the confounding effect of these variables since advanced age had a significant effect on the outcome variable and the male sex was more frequent in patients who underwent amputation. The accuracy of RDW as a predictor of amputation was calculated using a receiver operator characteristic (ROC) curve. The area under the curve, sensitivity, and specificity was determined by the ROC curve. The point in the ROC curve closest to the top-left of the ROC graph was determined as the optimal cutoff value for RDW. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients were presented in Table 1. Mean age in the amputation group was significantly higher than in the amputation group (58.4±9.3 *vs.* 67.2±9.1 years for limb salvage and amputation groups, respectively; p<0.001). Male sex was more common in the amputation group, but the difference between the groups was not significant (132 [65%] *vs.* 33 [78.6%] for limb salvage and amputation groups, respectively; p=0.08). Cerebrovascular disease

Table 1
Baseline clinical characteristics of the patients

	Limb salvage group (n=203)			Amputation group (n=42)			
Variables	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			58.4±9.3			67.2±9.1	**<0.001**
Sex							
Male	132	65		33	78.6		0.08
Diabetes	45	22.2		9	21.4		0.91
Hypertension	120	59.1		19	45.2		0.09
Coronary artery disease	61	30.0		8	19.0		0.14
Tobacco use	128	63.1		18	42.9		**0.01**
Chronic obstructive pulmonary disease	58	28.6		16	38.1		0.22
Cerebrovascular disease	27	13.3		16	38.1		**<0.001**
Renal failure	42	20.7		10	23.8		0.65
Site of arterial embolism							
Abdominal aorta	14	6.9		2	4.8		0.46
Iliac arteries	37	18.2		12	28.6		0.12
Femoral arteries	152	74.9		28	66.7		0.27
Recurrent embolism	41	20.2		18	42.9		**0.002**

SD: Standard deviation.

was significantly more common in the amputation group (27 [13.3%] *vs.* 16 [38.1%] for limb salvage and amputation groups, respectively; p<0.001), and tobacco use was significantly less common in the amputation group (128 [63.1%] *vs.* 18 [42.9%] for limb salvage and amputation groups, respectively; p=0.01). The proportion of patients requiring embolectomy due to recurrent embolism was significantly higher in the amputation group than in the limb salvage group (41 [20.2%] *vs.* 18 [42.9%] for limb salvage and amputation groups, respectively; p=0.002).

Of the 245 patients who underwent embolectomy for lower extremity embolism, 42 (17.1%) patients underwent amputation of the same limb; of these, 26 (10.6%) were major lower limb amputations (14 early in-hospital amputations, 12 postdischarge follow-up amputations), 16 (6.5%) were minor amputations (12 early in-hospital amputations, four postdischarge follow-up amputations).

Total blood count and biochemical parameters did not differ significantly between the limb salvage and amputation groups, except for the RDW (13.7±1.7% *vs.* 14.5±1.1%, p<0.001), platelet distribution width (22.3±12.7 *vs.* 24.2±14.0 fL, p=0.03), and urea (38.2±12.9 *vs.* 46.1±18.7 mg/dL, p=0.001, Table 2). The mean RDW was 13.80±1.17% in

Table 2
Comparison of baseline laboratory parameters of the patients

	Limb salvage group (n=203)	Amputation group (n=42)	
Variables	Mean±SD	Mean±SD	*p*
Hemoglobin (g/dL)	14.0±1.6	14.4±1.5	0.19
Hematocrit (%)	42.0±5.1	42.4±4.7	0.97
MCV (fL)	88.0±5.0	89.5±5.8	0.11
MCH (pg)	29.4±1.9	29.8±1.6	0.46
MCHC (g/dL)	33.2±1.0	33.4±1.0	0.23
RDW (%)	13.7±1.7	14.5±1.1	<0.001
Platelet count (K/uL)	261.6±66.4	252.6±88.2	0.15
MPV (fL)	8.2±1.1	8.2±1.1	0.71
PDW (fL)	22.3±12.7	24.2±14.0	0.03
WBC (K/uL)	8.2±2.2	7.8±3.3	0.10
Neutrophil count (K/uL)	5.3±1.9	5.0±2.1	0.19
Neutrophil percentage (%)	61.4±9.9	61.2±12.0	0.45
Lymphocyte count (K/uL)	2.2±0.7	2.0±0.6	0.08
Monocyte count (K/uL)	0.6±0.2	0.6±0.3	0.19
Glucose (mg/dL)	135.0±58.2	134.0±51.9	0.66
Urea (mg/dL)	38.2±12.9	46.1±18.7	0.001
Creatinine (mg/dL)	1.0±0.5	1.0±0.5	0.95
ALT (U/L)	26.3±15.6	27.3±23.1	0.39
AST (U/L)	24.5±12.1	23.0±13.6	0.08
PT	12.4±3.5	12.8±4.4	0.24
aPTT	33.7±12.1	42.3±47.3	0.11
Free T3 (pg/dL)	2.9±0.6	2.8±0.5	0.53
Free T4 (ng/dL)	1.3±0.5	1.4±0.5	0.98
TSH (μIU/mL)	1.8±1.1	1.7±1.4	0.31

SD: Standard deviation; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; WBC: White blood cell count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; TSH: Thyroid-stimulating hormone.

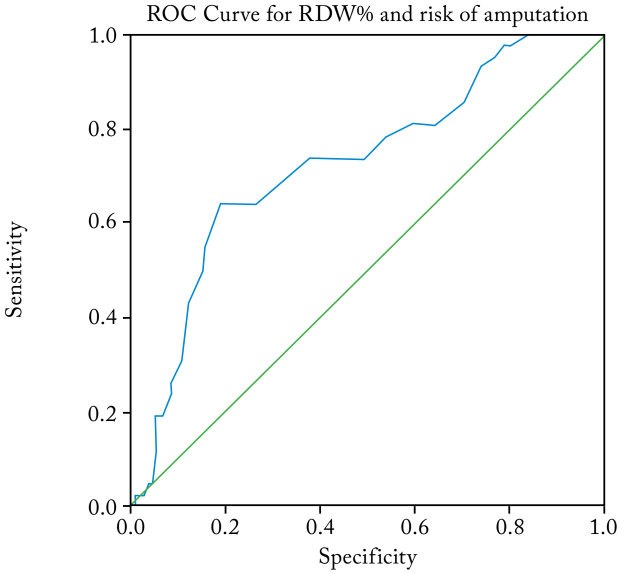

Figure 1. Receiver operating characteristics curve for RDW and risk of amputation.
ROC: Receiver operator characteristic; RDW: Red cell distribution width.

females and 13.85±1.83% in males (p=0.95). Receiver operating characteristics curve for RDW and risk of amputation revealed an area under the curve of 0.725 (95% confidence interval [CI]: 0.640-0.811, p<0.001) and an optimal cut-off value of 13.85% (sensitivity 69%, specificity 68%; Figure 1). Both visual inspection and the area under the curve value suggest that the fit of the model is in the acceptable range. The results suggest that the RDW score was efficient for identifying amputation.

In univariate (unadjusted) multinomial logistic regression analysis, age (odds ratio [OR]=1.131, 95% CI: 1.074-1.191, p<0.001), recurrent embolism in the same limb (OR=2.898, 95% CI: 1.238-6.780, p=0.01), urea level (OR=1.037, 95% CI: 1.013-1.062, p=0.003), and RDW (OR=1.324, 95% CI: 1.006-1.741, p=0.04) were significantly associated with the risk of major amputation, whereas the association of RDW with the risk of major amputation did not remain when adjusted for age and sex (OR=1.191,

Table 3
Univariate multinominal logistic regression analysis and multivariate multinomial logistic regression analysis adjusted for age and sex

	Univariate analysis unadjusted			Multivariate analysis (adjusted for age and sex)		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)						
Major amputation	1.131	1.074-1.191	<0.001			
Minor amputation	1.074	1.016-1.136	0.01			
Cerebrovascular disease						
Major amputation	1.956	0.721-5.306	0.18	0.559	0.174-1.799	0.33
Minor amputation	10.864	3.652-32.319	<0.001	9.296	2.723-31.734	<0.001
Recurrent embolism						
Major amputation	2.898	1.238-6.780	0.01	3.862	1.460-10.216	0.006
Minor amputation	3.073	1.080-8.742	0.03	3.726	1.260-11.024	0.01
Urea (mg/dL)						
Major amputation	1.037	1.013-1.062	0.003	1.038	1.010-1.066	0.006
Minor amputation	1.024	0.992-1.057	0.14	1.016	0.984-1.049	0.33
RDW (%)						
Major amputation	1.324	1.006-1.741	0.04	1.191	0.963-1.474	0.10
Minor amputation	1.239	0.907-1.691	0.17	1.131	0.859-1.489	0.38
PDW (fL)						
Major amputation	0.999	0.967-1.032	0.97	0.995	0.960-1.031	0.78
Minor amputation	1.024	0.991-1.059	0.14	1.029	0.994-1.065	0.10

OR: Odds ratio; CI: Confidence interval; RDW: Red cell distribution width; PDW: Platelet distribution width.

95% CI: 0.963-1.474, p=0.10). Age (OR=1.074, 95% CI: 1.016-1.136, p=0.01), cerebrovascular disease (OR=10.864, 95% CI: 3.652-32.319, p<0.001), and recurrent embolism (OR=3.073, 95% CI: 1.080-8.742, p=0.03) were significantly associated with the risk of minor amputation, and cerebrovascular disease (OR=9.296, 95% CI: 2.723-31.734, p<0.001) and recurrent embolism (OR=3.726, 95% CI: 1.260-11.024, p=0.01) remained significant even when adjusted for age and sex (Table 3). Post hoc power analysis revealed that, given an alpha error of 0.05, the two-tailed difference in mean RDW between groups yielded a statistical power of 89.39%.

DISCUSSION

This study aimed to test whether RDW can predict the risk of amputation in the early postoperative or midterm period in patients who underwent embolectomy for acute lower limb ischemia. The mean RDW in the amputation group was within the normal range but was significantly higher than that of the patients in the limb salvage group. In the univariate analysis, RDW was found to be a significant predictor of major amputation but not that of minor amputation. In the multivariate analysis adjusted for age and sex, this significant association was absent. The overall amputation (major and minor amputations or early and midterm amputations) sensitivity and specificity of RDW as a laboratory indicator was unsatisfactory.

It is controversial whether the ideal interventional treatment in acute lower limb ischemia is the use of evolving endovascular methods or the traditional surgical approach. Lukasiewicz,[9] in a recent study comparing the results of endovascular procedures and surgery/hybrid therapy in acute limb ischemia, reported that amputation and complication rates were comparable, six-month mortality was higher in those who underwent surgery, and the rate of reintervention was higher in those who underwent endovascular treatment. This study concludes that both modalities have an effective role in the contemporary management of acute lower limb ischemia, with two-thirds of all patients having arterial thrombus in the etiology (half underwent surgery) and embolism (86% underwent surgery) in the remaining. Surgery has been our routine approach in cases with arterial embolism from a distal source to the lower limb, and in the present study, we wanted to determine the prognostic role of RDW in this patient subgroup; our early amputation rate (n=26, 10.6%) was close to the rate reported after surgery in the above study (8.9%).

Several studies have addressed clinical and demographic risk factors for amputation following acute lower limb ischemia, but the parameters reported were varied. In a recent epidemiological study, the one-year amputation rate was as high as 46%, and high-grade ischemia, the female sex, age, and anemia were associated with a higher risk of amputation. In addition, this study reported that the amputation rate in individuals living at a nursing home was 100%.[1] There were also studies reporting that delayed surgical intervention after admission significantly increased the risk of amputation.[7,14] In our study, recurrent embolism in the related limb and urea level appeared to be significant predictors of both major and minor amputations, even when adjusted for age and sex.

Red cell distribution width reflects the erythrocyte size distribution and is routinely calculated in the total blood count. Although it is used in the differential diagnosis of anemia, it has been shown to be correlated with fragility and vulnerability in individuals with systemic disease. Therefore, its usefulness in calculating cardiovascular risk has recently been the focus of research.[15] Talarico et al.,[10] in a retrospective study, found that the highest RDW tertile was independently associated with increased risk of all-cause death (hazard ratio [HR]=2.73, 95% CI: 1.63-4.5) and composite end point (adjusted HR=2.23, 95% CI: 1.53-3.24), (Cox regression, median follow-up: 3.78 years), proposing that RDW is a good prognostic marker for cardiovascular mortality. Others reported that the increased values of RDW were significantly associated with several cardiovascular outcomes, including coronary calcium score and related cardiovascular risk,[11] periprocedural myocardial infarct in patients receiving elective percutaneous coronary intervention,[16] mortality due to carotid atherosclerosis,[17] and stroke risk.[18]

A survey study demonstrated that RDW is an independent predictor of the risk of developing peripheral artery disease. The study determined that even when multiconfounding adjustment was made, each unit increase in the RDW increased the risk of peripheral arterial disease. Finding Odd's ratio 1.9 was a numerical indicator of this. In fact, the high quartile RDW was found to significantly improve the predictive accuracy of peripheric arterial disease screening criteria.[14] Ye et al.,[19] in a study in which they followed 13,039 patients with peripheral artery disease, showed that patients in the highest quartile of RDW had a 66% higher overall mortality than those in the lowest quartile (after adjustment for age, sex, cardiovascular risk factors, and comorbidities). Another more recent study suggested that an RDW level above the 75th percentile (>14.1%) is an independent predictor of peripheral artery disease presence and complexity (TASC [TransAtlantic InterSociety Consensus] C and D).[20] Although these studies reliably indicate that RDW levels are indicative of the presence and prognosis of lower extremity ischemic artery disease, none of them have addressed whether RDW levels are associated with limb salvage after acute lower limb ischemia.

Since the cut-off value we found (13.85%) for the prediction of overall (major and minor) amputation is in the normal range, it may not have prognostic significance alone in patients presenting with acute lower limb ischemia. Red cell distribution width is used in routine clinical practice in the differential diagnosis of vitamin B12 deficiency, folic acid deficiency, and other megaloblastic anemias with macrocytosis. Therefore, RDW can be affected by the level of these substances. Moreover, although the upper limit of RDW is reported as 14.0%, this value is an instrument-specific value and may vary according to the standards of each laboratory. In addition to these, considering that RDW is affected by acute inflammation, white blood cell count, and even lipid profile, it can only aid other prominent risk factors in calculating the risk of amputation after acute limb ischemia.[21]

The main limitation of the present study was its retrospective design. In a prospective and match-controlled study, the deviation of RDW from the normal value could be calculated, and a more accurate effect size could be obtained. Another limitation of the study was that the operations were performed by different surgeons, which may have affected the patency. The inability to include amputation-free survival rates in the risk calculation due to the short follow-up period is one of the limitations that should be noted. Because of the heterogeneity in our patient group, RDW levels may not have accurately predicted the risk of amputation in our study. A larger study in a more homogeneous group is required.

In conclusion, RDW may have a role in the prediction of adverse outcomes in patients treated for acute lower limb ischemia; however, since amputation is associated with many confounders and RDW levels are affected by certain clinical parameters, it cannot be used as a stand-alone predictive marker. Future studies on risk assessment in amputation are needed, in which the confounders are adjusted and the RDW values are calibrated with a control group sampled at the same health center, to determine the optimal cut-off value or percentile of RDW.

Ethics Committee Approval: The study protocol was approved by the Türkiye Yüksek Ihtisas Education and Research Hospital Education Planning Board (date: 23.09.2014, no: 12631). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Data collection and/or processing, analysis and/or interpretation, literature review, writing the article, critical review, references and fundings: S.S.; Idea/concept, design: I.T.

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