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# The value of the SUV ratio between lymph node and bone marrow in predicting pelvic lymphatic metastasis of patients with locally advanced cervical cancer: an integrated PET/CT study

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***Purpose*** **This study aimed to evaluate the value of the standardized uptake value (SUV) ratio between lymph nodes and bone marrow (BM) measured by Fluorine-18-fluorodeoxyglucose PET and computed tomography ($^{18}$F-FDG PET/CT) for predicting pelvic lymph node (PLN) metastasis in patients with locally advanced cervical cancer (LACC).**

***Materials and methods*** **A total of 62 patients with pathological stage Ib-IVa cervical cancer who underwent $^{18}$F-FDG PET/CT before treatment were reviewed retrospectively. We measured the metabolic and morphological parameters of lymph nodes and primary tumors, bone marrow SUV (SUVBM) and calculated the ratio of lymph nodes maximum SUV (SUVmax) to bone marrow SUV (SUVLN/BM) and the ratio of short-axis diameter to long-axis diameter (Ds/l) of lymph nodes. A receiver operating characteristic (ROC) curve was performed to evaluate the diagnostic efficacy of each parameter.**

***Results*** **There were 180 lymph nodes with pathological evidence included in the study. Our results indicated that Ds/l, SUVmax of lymph nodes (SUVLN) and SUVLN/BM were independent risk factors for PLN metastasis in LACC ($P<0.05$), and SUVLN/BM showed the best diagnostic performance by ROC curve analysis. The SUVBM in the anemia group was significantly higher than that in the nonanemia group (3.05 vs. 2.40, $P<0.05$); furthermore, false-positive cases decreased when the SUVLN/BM was used as the diagnostic criterion instead of SUVLN, especially in the anemia group. ROC curve analysis showed that the area under the curve value of the combination of SUVLN/BM and Ds/l was 0.884 ($P<0.05$), which was higher than Ds/l or SUVLN/BM alone.**

***Conclusions*** **SUVLN/BM could improve the ability to predicting PLN metastasis in patients with LACC, and the diagnostic efficacy of the combination of SUVLN/BM and Ds/l might be better than that of a single parameter.**
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**Keywords:** **$^{18}$F-FDG PET/CT, locally advanced cervical cancer, metastasis, pelvic lymph node**

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## Introduction

Cervical cancer is the fourth most common malignant tumor in women worldwide [1], and more than 60% of the newly diagnosed patients were diagnosed with locally advanced cervical cancer (LACC) [2]. Extra-cervical invasion of cervical cancer is mainly through the lymph node pathway, and the pelvic lymph node (PLN) is the most common metastatic site. The assessment of lymph node by imaging or pathological examination is integrated into the latest International Federation of Gynecology and Obstetrics (FIGO) staging system [3]. Therefore, it is extremely important to predict PLN metastasis accurately for the treatment strategy and prognosis in patients with LACC.

Preoperative evaluation of PLN of cervical cancer mainly depends on imaging examination. Traditional imaging examinations, such as computed tomography (CT) and MRI, usually base the identification of metastatic nodes on node size measurements, a short-axis diameter greater than 10 mm is the most accepted criterion [4]. However, the size of lymph node does not always correlate with their tumor involvement [5,6]. Fluorine-18-fluorodeoxyglucose PET and computed tomography ($^{18}$F-FDG PET/CT), with the dual advantages of anatomical positioning and functional imaging, has been widely used in the diagnosis, staging and prognosis evaluation of various tumors; recently, it tends to be the best imaging method to detect lymph node metastasis [7]. Some semiquantitative metabolic parameters of $^{18}$F-FDG PET/CT, especially the maximum standard uptake value ($SUV_{max}$), have proved to be valuable in the diagnosis of lymph node metastasis [8,9]. However, high uptake



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of $^{18}$F-FDG can be also seen in benign or inflammatory lymph node, which has resulted in false-positive results [10–14]. Thus, many researchers turned their attention to other metabolic parameters. For example, some investigators used the SUV ratio of lymph node to the primary tumor, mediastinum or liver to predict mediastinal lymph node metastasis to eliminate the influence of blood glucose, weight, reconstruction technology, noise, as also as background hypermetabolism caused by systemic inflammation or other [15–17]. Similar methods have been used in cervical cancer. For example, a study had shown that the SUV ratio of lymph node to the primary tumor is an independent predictor of cervical cancer recurrence [18]. Another study showed that the SUV ratio of the lymph node to pelvic blood pool was related to extractive recurrence free-survival [19]. There were some studies indicated that increased bone marrow $^{18}$F-FDG uptake was caused by systemic inflammation [20,21] and anemia [22,23]. To our knowledge, vaginal bleeding is the most common symptom in patients with cervical cancer that could result in anemia. But so far, there have been no studies showing that anemia leads to the high uptake of FDG in the lymph node. If we assume that anemia will lead to high FDG uptake in the lymph node, will the SUVLN/bone marrow (BM) have better diagnostic efficacy than the SUV lymph node (SUVLN)?

In addition, some researchers have proposed a 'combined diagnosis' method based on $^{18}$F-FDG PET/ CT to improve the diagnostic efficiency of lymph node metastasis, and these results proved that the combination of metabolic parameters and morphological parameters can better predict lymph node metastasis for patients with lung cancer [24,25] and cervical cancer [26].

The purpose of this study was to assess the predictive ability of the SUVLN/BM for PLN metastasis in patients with locally advanced cervical cancer, and to explore whether it can reduce false-positive cases; and further evaluate the diagnostic value of the combination of morphological parameters (lymph node diameter based on CT) and metabolic parameters (SUVLN/BM-derived from SUV based on PET); moreover, this study is the first time to apply the ratio of the lymph node $SUV_{max}$ to bone marrow SUV to predict PLN metastasis of cervical cancer.

## Materials and methods

### Patients

This retrospective analysis included 62 patients diagnosed with LACC between July 2017 and June 2021, who underwent $^{18}$F-FDG PET/CT examination before receiving any therapy. The inclusion criteria were as follows: (1) LACC confirmed in all patients by cytology or histopathology; (2) radical resection of cervical cancer and pelvic lymph node dissection were performed within 1 month after PET/CT examination; (3) staged IB-IVA according to FIGO stage system (2018) [3] and (4) no systemic inflammation and other tumors. Patients who conducted blood routine examination within 1 week before PET/CT examination were divided into the anemia group and the nonanemia group. Anemia is defined as hemoglobin level <120 g/L in females according to the WHO criteria [27].

### $^{18}$ F-FDG PET imaging protocol

All patients underwent PET/CT scan (Discovery PET-CT 710, GE Healthcare, USA); $^{18}$F-FDG is produced by our medical cyclotron, radiochemical purity >95%. The patients fasted for at least 6 h, and the glucose levels in the peripheral blood were <120 mg/dl before $^{18}$F-FDG injections. The CT and PET data were acquired for the proximal thigh towards the base of the skull, 60 min after the injection of a weight-adjusted dose of 3.70–5.55 MBq/kg. After the initial low-dose CT (120 kV, 100 mA, noise index 18, thickness 3.75 mm), conventional PET imaging with an acquisition time of 2.5 min/bed position in a 3-dimensional (3D) mode was conducted. The images were reconstructed using iterative methods.

### $^{18}$ F-FDG PET image analysis

All PET and CT images were analyzed by volume viewer 4.6 in an AW workstation (GE Healthcare). The morphological and metabolic parameters of the primary lesion and lymph node were measured by two experienced nuclear medicine physicians, such as primary tumor maximum SUV (SUVT), primary tumor metabolic volume (MTVT), primary tumor total glycolysis (TLGT), SUVBM, SUVLN, the maximum diameter of the primary tumor (DT), short-axis diameter of lymph node (Ds) and long-axis diameter of lymph node (Dl). To measure FDG uptake of the BM, a volume of interest (VOI) was drawn over the vertebral body of each of five vertebrae (L3-5 and S1-2 spines, unless a pathologic condition such as compression fracture or severe osteoarthritic changes was present). The mean SUV of each VOI was measured using an automatic contour set at 75% of the maximum SUV because the 75% cutoff value of the maximum SUV showed good reproducibility between subjects for measuring the most representative of the lesions. The mean SUV of the four selected vertebrae was calculated and defined as SUVBM [28–30]. SUVLN/T and SUVLN/BM are the $SUV_{max}$ ratios of lymph node to primary lesion and the ratio of lymph node $SUV_{max}$ to SUVBM; Ds/l is the ratio of short-axis diameter to long-axis diameter of lymph node.

### Statistical analysis

The semiquantitative parameters of primary tumor and lymph node were quantitative data; The data of normal distribution were expressed as mean ± SD ($x \pm s$), and the data of abnormal distribution is expressed as the medians (P25, p75). To compare the statistical difference of

quantitative parameters between the group with lymphonodus metastasis and without lymphonodus metastasis, the *t*-test was used for normal distribution data, while the Mann-Whitney U test was used for abnormal distribution data. Binary logistic regression analysis was applied to select predictive factors of lymph node metastasis. The receiver operating characteristic (ROC) curve was used to analyze the diagnostic efficacy of PET/ CT parameters in lymph node metastasis. All statistical tests were performed using IBM SPSS software, version 22.0, and differences were presumed to be significant when the *P* value was <0.05.

## Results

### General characteristics of patients

Among the 62 patients with LACC, the median age was 51.0 (range, 23–68) years. There were 59 cases of squamous cell carcinoma (95.2%) and three adenocarcinomas (4.8%). According to the FIGO stage system, 13 (21.0%) were reported as stage I, 14 (22.6%) stage II, 30 (48.4%) stage III and 5 (8.0%) stage IV. In total 28 patients (45.2%) were confirmed to have metastasis in lymph node through postoperative pathology and 34 (54.8%) have no metastasis in lymph node. The patients' characteristics were summarized in Table 1.

### Lesion-based comparison between metastatic and nonmetastatic lymph node

A total of 180 lymph nodes were identified by pathology in the study, including 80 metastatic lymph nodes and 100 nonmetastatic lymph nodes. The median of Ds, Ds/l, SUVLN, SUVLN/T and SUVLN/BM in metastatic lymph node were significantly higher than those in nonmetastatic lymph node (all $P<0.05$). The median of the Ds/l in metastatic lymph node and in nonmetastatic lymph node were 0.80 and 0.70, SUVLN were 3.90 and 2.40 and SUVLN/BM were 1.80 and 0.90, respectively (Table 2).

### Diagnostic performance of PET/CT quantitative parameters and combined parameters

The ROC curves analysis (Table 3) revealed that the area under the curve (AUC) value of Ds, Ds/l, SUVLN, SUVLN/T and SUVLN/BM were 0.685 (95% CI, 0.602–0.767), 0.725 (95% CI, 0.646–0.805), 0.787 (95% CI, 0.714–0.853), 0.784 (95% CI, 0.718–0.857) and 0.852 (95% CI, 0.793–0.910), respectively, all $P<0.05$, and the cutoff values were 1.05, 0.75, 3.35, 0.25 and 1.45, respectively. The AUC value of Ds/l was greater than Ds, and SUVLN/BM was greater than SUVLN and SUVLN/T, which showed that the diagnostic efficiency of Ds/l for PLN metastasis was better than Ds in morphological parameters, and SUVLN/BM was better than SUVLN and SUVLN/T among metabolic parameters. the diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the SUVLN/BM were 68.8, 87.5, 78.1, 84.6 and 73.7%, respectively. The AUC value of the combination of SUVLN/BM and Ds/l was 0.884 (95% CI, 0.832–0.935; $P<0.05$), which was higher than Ds/l or SUVLN/BM alone (Fig. 1). The diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the combination of SUVLN/BM and Ds/l were 75.0, 87.5, 81.3, 85.7 and 77.8%, respectively.

**Table 1** Patient characteristics

| Characteristic | *n* (%) | *P* value |
|---|---|---|
| Age (median) (years) | 51 | 0.856 |
| Age (range) (years) | 23–68 | |
| Pathological type | | 0.863 |
| Squamous carcinoma | 59 (95.2) | |
| Adenocarcinoma | 3 (4.8) | |
| FIGO stage | | <0.001 |
| I | 13 (21.0) | |
| II | 14 (22.6) | |
| III | 30 (48.4) | |
| IV | 5 (8.0) | |
| Lymphatic metastasis | | |
| Yes | 28 (45.2) | |
| No | 34 (54.8) | |

FIGO, International Federation of Gynecology and Obstetrics.

### Univariate and multivariate logistic regression model for predicting pelvic lymph node metastasis

The results of the logistic regression model for predicting PLN metastasis are shown in Table 4. Univariate analysis revealed that Ds, Ds/l, SUVLN, SUVLN/T and SUVLN/BM were significantly associated with PLN metastasis, whereas in multivariate analysis, only Ds/l ( odds ratio [OR] = 2.302; 95% CI, 1.205–5.697; $P=0.001$), SUVLN (OR = 2.974; 95% CI, 1.386–4.933; $P=0.026$), SUVLN/BM (OR, 3.280; 95% CI, 1.696–5.280; $P=0.001$) were statistically significant predictors for PLN metastasis.

### Patient-based comparison of SUVBM in anemia group and nonanemia group

The average value of SUVBM in the anemia group ($n=20$) and nonanemia group ($n=38$) were 3.05 and 2.40 ($P=0.01$), respectively. When SUVLN/BM and SUVLN were used as diagnostic criteria for PLN metastasis, the number of false-positive diseases was 10 and 22, respectively, of which the number of false-positive diseases in the anemia group was 4 and 13, respectively, and the number of false-positive diseases in the nonanemia group was 6 and 9 respectively ($P=0.26$).

## Discussion

This study showed that the SUVLN/BM, derived from SUV on PET, is a useful predictor for PLN metastasis in patients with LACC, and may result in the reduction of false-positive cases; the combination of SUVLN/BM and Ds/l derived from lymph node size on CT could improve the diagnostic efficiency of PLN metastasis in patients with LACC.

In our study, SUVLN/BM, the SUV ratio of the lymph node to bone marrow, showed the best diagnostic performance

**Table 2 Comparison of parameters on $^{18}$F-FDG PET/CT between metastatic and nonmetastatic lymph nodes**

| | LNM (–) | | LNM (+) | | |
|---|---|---|---|---|---|
| Variables | (*n*=100) | | (*n*=80) | | *P* value |
| Primary tumor | | | | | |
| DT(cm) | 4.26 | ±1.39 | 4.30 | ±1.65 | 0.915 |
| SUVT | 15.25 | (11.29, 20.31) | 14.70 | (9.93, 18.71) | 0.692 |
| MTVT($cm^3$) | 11.60 | (5.91, 18.56) | 17.00 | (9.14, 31.91) | 0.052 |
| TLGT | 89.70 | (43.36, 231.28) | 131.20 | (86.11, 376.14) | 0.121 |
| SUVBM | 2.75 | (2.29, 3.10) | 2.45 | (2.20, 2.91) | 0.232 |
| Lymph node | | | | | |
| Ds(cm) | 0.60 | (0.50, 0.80) | 0.80 | (0.60, 1.10) | <0.001 |
| Dl(cm) | 1.00 | (0.90, 1.28) | 1.00 | (0.80, 1.45) | 0.053 |
| Ds/l | 0.70 | (0.60, 0.80) | 0.80 | (0.70, 0.90) | <0.001 |
| SUVLN | 2.40 | (1.90, 3.40) | 3.90 | (2.90, 6.00) | <0.001 |
| SUVLN/T | 0.20 | (0.10, 0.20) | 0.30 | (0.20, 0.50) | <0.001 |
| SUVLN/BM | 0.90 | (0.70, 1.20) | 1.80 | (1.20, 2.30) | <0.001 |

BM, bone marrow; DT, the maximum diameter of the primary tumor; Ds, short-axis diameter of LN; D1, long-axis diameter of LN; LN, lymph node; LNM, lymph node metastasis; MTVT, primary tumor metabolic volume; SUV, standardized uptake value; SUVT, primary tumor maximum SUV; TLGT, primary tumor total glycolysis.

**Table 3 Diagnostic performance of $^{18}$F-PET/ CT quantitative parameters and combined parameters**

| Variables | AUC | 95% CI | *P*-value | Cutoff value | Sensitivity % | Specificity % | Accuracy% | NPV% | PPV% |
|---|---|---|---|---|---|---|---|---|---|
| Ds | 0.685 | 0.602–0.767 | <0.001 | 1.05 | 30.00 | 97.50 | 63.75 | 92.31 | 58.21 |
| Dl | 0.529 | 0.437–0.620 | 0.0553 | 1.45 | 25.00 | 92.50 | 58.75 | 76.92 | 55.22 |
| Ds/l | 0.725 | 0.646–0.805 | <0.001 | 0.75 | 68.75 | 68.75 | 68.75 | 68.75 | 68.75 |
| SUVLN | 0.787 | 0.714–0.853 | 0.001 | 3.35 | 70.00 | 72.50 | 71.25 | 71.79 | 70.73 |
| SUVLN/T | 0.784 | 0.718–0.857 | <0.001 | 0.25 | 63.75 | 78.75 | 71.25 | 75.00 | 68.48 |
| SUVLN/BM | 0.852 | 0.793–0.910 | <0.001 | 1.45 | 68.75 | 87.50 | 78.13 | 84.62 | 73.68 |
| Combination | 0.884 | 0.832–0.935 | <0.001 | | 75.00 | 87.50 | 81.25 | 85.71 | 77.78 |

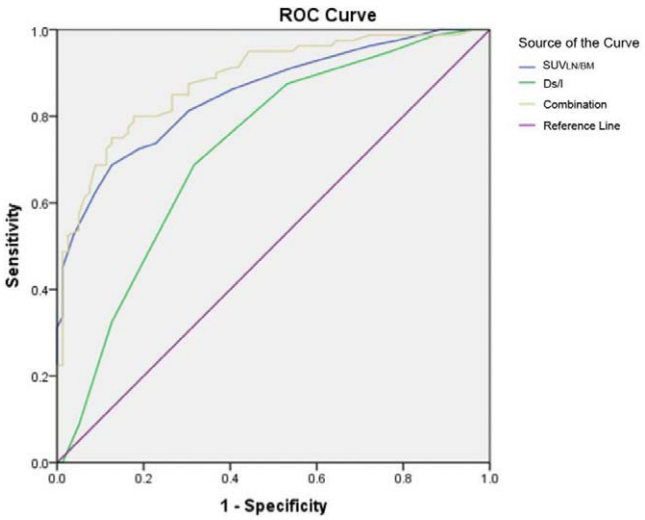
AUC, area under the curve; BM, bone marrow; CI, confidence interval; Ds, short-axis diameter of LN; D1, long-axis diameter of LN; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value; SUV, standardized uptake value.

among all parameters. In previous studies, the SUV ratio of lymph node to primary tumors, mediastinum or liver was considered to be more valuable in predicting lymph node metastasis of lung cancer and breast cancer [16,17,31]. For example, in a study involving 136 breast cancer patients, Park *et al.* [31] found that the $SUV_{max}$ ratio of lymph node to primary tumor could predict axillary lymph node metastasis better than the $SUV_{max}$ of lymph node. In another study, Kuo *et al.* [16] found that lymph node/mediastinal blood pool and lymph node/liver SUV ratios improved the detection of N2 metastases in patients with nonsmall cell lung cancer compared with SUVLN. There are a few similar studies on patients with cervical cancer. Brunette *et al.* [19] used the normalization of lymph node $SUV_{max}$ (SUV ratio of lymph node to pelvic blood pool) to predict lymph node metastasis of cervical cancer, and the results showed that the standardized SUV did not increase the diagnostic accuracy, but was related to extractive recurrence free-survival. In addition, a study has shown that SUVLN/T is an independent predictor of cervical cancer recurrence [18]; however, our study showed that SUVLN/T is not an independent predictor of PLN metastasis of cervical cancer. SUVLN(the $SUV_{max}$ of lymph node) was commonly used to distinguish between benign and malignant lymph node [9]. Our study showed higher SUVLN and SUVLN/BM both increased the risk of metastasis (HR = 2.974, 3.280; $P < 0.05$), and the diagnostic efficiency of SUVLN/BM was to be better than SUVLN in this study, which may be related to a large proportion of anemia patients in this study. The SUVLN/BM, as a diagnostic index was applied to predict PLN metastasis of cervical cancer for the first time in our study, and more research are needed to confirm the role of SUVLN/BM.

Previous studies have suggested that anemia could cause the FDG uptake of BM [22,23], and this study also confirmed that SUVBM in the anemia group was significantly higher than that in the nonanemia group ($P < 0.05$). Moreover, false-positive cases decreased when the SUVLN/BM was used as the diagnostic criterion instead of SUVLN for PLN metastasis, and the decreasing degree of false-positive cases in the anemia group was higher than that in the nonanemia group, Unfortunately, there is no statistical difference in the false-positive rate between the anemia group and the nonanemia group with different diagnostic criteria (SUVLN and SUVLN/BM) ($P = 0.267$)($P = 0.267$), whose reason may be attributed to the small sample size of the anemia subgroup. Therefore, more data are needed to affirm this in the future.

Ds/l as a morphological parameter on CT is also a potential parameter to predict lymph node metastasis in this study. Short-axis diameter greater than 10 mm is the most accepted criterion in traditional imaging examination [32,33]. Li *et al.* [26] hold that although the overall diagnostic efficacy of Ds/l alone is limited it provides a certain contribution to reduce false-negative cases. Ds/l is better

**Fig. 1**




Receiver operating characteristic (ROC) curve analysis of SUVLN/BM, Ds/l and the combination for the diagnosis of pelvic lymph node metastasis. BM, bone marrow; LN, lymph node; SUV, standardized uptake value.

**Table 4 Univariate and multivariate logistic regression model for predicting pelvic lymph node metastasis**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Variables | OR (95% CI) | *p*-value | OR (95% CI) | *P* value |
| Ds | 5.749 (1.497–10.328) | <0.001 | | |
| DI | 1.069 (0.893–3.173) | 0.050 | | |
| Ds/l | 8.396 (1.697–11.023) | <0.001 | 2.302 (1.205–5.697) | 0.001 |
| SUVLN | 2.158 (1.780–2.976) | 0.001 | 2.974 (1.297–4.933) | 0.026 |
| SUVLN/BM | 3.011 (1.982–8.964) | <0.001 | 3.284 (1.696–5.280) | 0.001 |
| SUVLN/T | 8.933 (3.873–12.258) | <0.001 | | |

BM, bone marrow; CI, confidence interval; Ds, short-axis diameter of LN; D1, long-axis diameter of LN; LN, lymph node; OR, odds ratio; SUV, standardized uptake value.

than DS and becomes the best morphological parameter to predict PLN metastasis of cervical cancer in our study.

In our study, the diagnostic efficacy of the combination of SUVLN/BM and Ds/l was better than that of any single parameter. Li *et al.* [26] revealed the combination diagnosis method that can better predict PLN metastasis for patients with early-stage cervical cancer, and the results coincide with our research, However, their study showed that the combination of primary tumor metabolic parameter and the morphological parameter is helpful to evaluate lymph node metastasis, whereas our study showed the combination of lymph node metabolic parameters and morphological parameters is helpful to evaluate lymph node metastasis. Our study showed that the metabolic parameters of the primary tumor are not related to lymph node metastasis, these differences may be related to different constituent samples, such as tumor stage, pathological type, and so on.

However, this study had several limitations. First, this study is a retrospective study, and it was conducted at a single institution with a limited number of cases and a small proportion of anemia, therefore, prospective, multicenter and large sample studies are essential to further confirm these results. Second, the measurements of metabolic parameters and nodal size were made in every case also including traditional normal-sized nodes, implying a large workload requires a large amount of time.

## Conclusion

This study suggested SUVLN/BM, a metabolic parameter derived from SUV on $^{18}$F-FDG PET, could improve the ability to predict PLN metastasis in patients with LACC and might reduce the false-positive cases; the diagnostic efficacy of the combination of the metabolic parameter derived from SUV based on $^{18}$F-FDG PET and the morphological parameter based on CT could better than that of a single parameter.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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