

Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Predicting Death Risk in Patients with Severe Hand, Foot and Mouth Disease

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Introduction: Severe hand, foot, and mouth disease (HFMD) may lead to serious complications, which cause child mortality during outbreaks. The aim of this study was to determine whether neutrophil-to-lymphocyte ratio (NLR) can predict death risk in severe HFMD.

Methods: Medical records for 664 severe HFMD patients were retrospectively examined, and NLR was calculated from blood counts. Youden's index was calculated to determine the optimal NLR cutoff. Uni- and multivariate logistic regression were used to determine death risk factors associated with severe HFMD.

Results: An NLR cutoff value of 2.01 and 2.50 respectively predicted mortality among all 664 severe HFMD and 137 critical HFMD. Among all 664 patients, the multivariate model identified the following as independently associated with death risk: high fever (OR 3.342, 95% CI 1.736–6.432), EV71 infection (OR 3.200, 95% CI 1.529–6.698), fasting glucose (OR 37.343, 95% CI 18.616–74.909), and NLR (>2.01) (OR 2.142, 95% CI 1.125–4.079). Among 137 critical HFMD, EV71 infection (OR 3.441, 95% CI 1.132–10.462), fasting glucose (OR 14.173, 95% CI 4.920–40.827), and NLR (>2.50) (OR 4.166, 95% CI 1.570–11.051) were associated with death risk.

Conclusion: In conclusion, NLR (>2.01) in severe HFMD and NLR (>2.50) in critical HFMD patients may be associated with increased death risk.

Keywords: enterovirus 71, hand, foot and mouth disease, neutrophil-to-lymphocyte ratio, risk factor

Introduction

Hand, foot and mouth disease (HFMD) is a common acute infectious disease caused by a variety of human enterovirus. It usually affects infants and children and typically involves fever, painful mouth sores and a skin rash, among other symptoms.¹ Most children with HFMD have mild symptoms, but some children with severe disease can suffer life-threatening complications, such as encephalitis, acute pulmonary oedema and cardiopulmonary failure. HFMD in such patients can progress rapidly with high morbidity and mortality.^{2–4}

Most HFMD patients are given symptomatic treatments and effective therapies are lacking. From 2008 to 2019, 24 million HFMD infections in children were reported in China, approximately 45% of which were associated with enterovirus 71 (EV71). This virus accounted for nearly all 3735 fatal infections during that period, based on data from the National Health Commission (www.chinacdc.cn).

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HFMD outbreaks and the associated high mortality have caused an important public health problem in China.^{5,6} It is therefore important to search for factors that can be assessed at a patient's first clinical visit to predict whether he or she will develop severe or life-threatening illness. This would aid clinical decision-making and disease management.

Markers of inflammation may be useful for predicting prognosis of HFMD patients, since children with severe HFMD show perturbations of cellular and humoral immunity. One candidate marker is the neutrophil-to-lymphocyte ratio (NLR), which is measured routinely in peripheral blood and serves as an index of systemic inflammation.⁷ The NLR is calculated by dividing the neutrophil count by the lymphocyte count.⁸ NLR is already used as an easily accessible inflammatory marker in adults with acute respiratory distress syndrome,⁹ spontaneous bacterial peritonitis,¹⁰ ischaemic heart disease, metabolic disease, cancer and other medical conditions.¹¹ In children, NLR can differentiate between viral and bacterial pneumonia,^{12,13} and it can be a useful diagnostic marker of acute appendicitis and acute infection.^{12,14} NLR may also correlate positively with other commonly used inflammatory markers.

Here we conducted what appears to be the first investigation of whether NLR has prognostic potential in HFMD. In this large retrospective study, we analysed the relationship of NLR with severe HFMD-associated death.

Materials and Methods

Study Population

This retrospective study analysed medical records of 664 Chinese patients with severe HFMD who were admitted to Xi'an Jiaotong University Second Affiliated Hospital or to Xi'an Children's Hospital between January 2012 and October 2016. Among the 664 patients with severe HFMD, 137 were diagnosed with critical HFMD and 97 died. This study was approved by the Medical Ethics Committees at both hospitals.

Patients were diagnosed with HFMD using the Hand, Foot and Mouth Disease Clinical Guide (2010 edition) issued by the National Health Commission of the People's Republic of China.¹⁵ These guidelines define HFMD in terms of symptoms and signs occurring during epidemics in preschool children, as well as the presence of typical exanthema on the hands, feet, mouth and/or buttocks, with or without fever. Patients were diagnosed with

mild HFMD if they had rashes on their hands, feet, mouths, and/or buttocks, with or without fever. Patients were diagnosed with severe HFMD if they had neurological, respiratory or circulatory manifestations. Patients were diagnosed with critical HFMD if they showed (1) frequent convulsions, coma or cerebral hernia; (2) dyspnoea, cyanosis, bloody frothy sputum, or pulmonary rales; or (3) shock and circulatory failure. We have excluded from other underlying diseases.

Data Collection

The ethics committees of the hospitals approved the protocol for the study and all patient data accessed complied with relevant data protection and privacy regulations. Detailed demographic data including age, sex and clinical characteristics were independently extracted from medical records by three authors (LYP, ZS, DHL). Data on clinical manifestations were collected, which included peak fever temperature; vomiting; and neurological, respiratory, and circulatory manifestations. Laboratory data at the time of admission were collected on enterovirus infection, procalcitonin (PCT), white blood cell (WBC) count, fasting glucose, and NLR.

Statistical Analysis

All statistical analyses were performed using SPSS 17.0 (IBM, Chicago, IL, USA). Continuous variables were summarised as mean \pm SD or median (range), and differences were assessed for significance using the Wilcoxon rank-sum test or Student's *t* test. Categorical variables were summarised as numbers and percentages, and differences between cases (patients who died from HFMD) and controls (patients who survived) were assessed for significance using the χ^2 test. Patients who survived served as the reference group for calculating odds ratios (ORs) and associated 95% confidence intervals (95% CIs). Univariate and multivariate logistic regression analyses were used to identify death risk factors associated with severe or critical HFMD. Receiver operating characteristic (ROC) curves were generated to define optimal NLR cutoff values. Significance for all statistical tests was defined to be $P < 0.05$.

Results

Patient Characteristics and Risk Factors for Severe HFMD

This study involved 664 patients diagnosed with severe HFMD (Table 1), ranging in age from 6 months to 72

Table 1 Clinicodemographic Characteristics of Patients with Severe HFMD

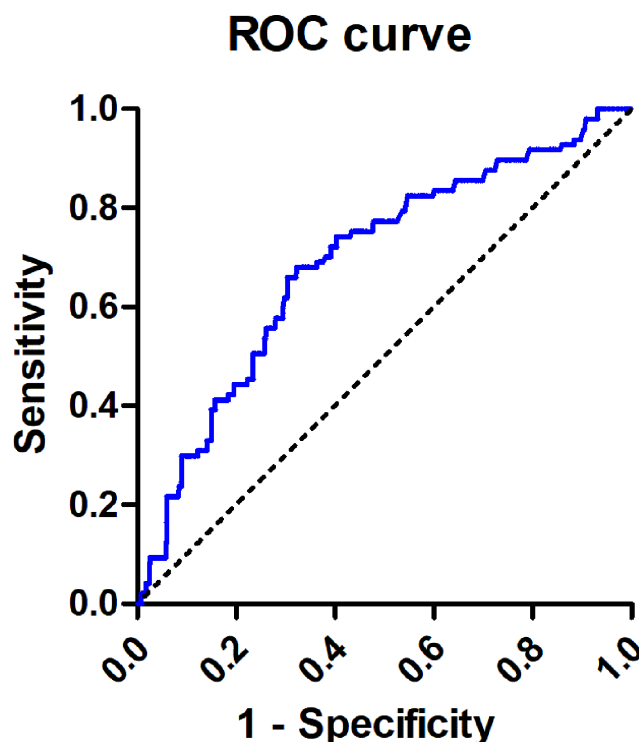
Characteristics	Survived (n=567)	Died (n=97)	P
Male/Female	359/208	59/38	0.639
Age, yr			0.006
≤3	439 (77.4)	87 (76.8)	
>3–6	128 (22.6)	10 (20.2)	
Rash	567 (100.0)	97 (100.0)	–
Fever	566 (99.8)	97 (100.0)	–
Duration of fever >3 d	448 (79.2)	72 (74.2)	0.276
Temperature (°C)			<0.001
37.3 to ≤38	60 (10.6)	0 (0)	
38–39	218 (38.4)	19 (19.6)	
39–40	289 (51.0)	78 (80.4)	
Hypersomnia	458 (96.6)	91 (93.8)	0.190
Hyperarousal	294 (62.0)	91 (93.8)	<0.001
Limb shaking	392 (82.7)	83 (85.6)	0.492
Convulsion	99 (20.9)	18 (18.6)	0.605
Vomiting	350 (61.7)	64 (66.0)	0.425
Pathologic reflexes	562 (99.1)	97 (100.0)	–
Dyspnea	36 (6.30)	97 (100.0)	–
Circulatory disturbance	40 (7.05)	97 (100.0)	–
PCT (>0.20 ng/mL)	243 (42.9)	49 (50.5)	0.160
NLR, median (range)	1.92 (0.20, 19.35)	3.43 (0.62, 13.85)	<0.001
NLR, mean±SD	2.69 ± 2.44	4.17 ± 2.81	–
NLR (≤3 yr, n=526)	2.43 ± 2.20	3.91 ± 2.73	<0.001
NLR (3–6 yr, n=138)	3.63 ± 2.94	6.46 ± 2.63	<0.001
NLR>2.01	271 (47.8)	75 (77.3)	<0.001
Fasting blood glucose level > 8.3 mmol/L	78 (13.8)	86 (88.7)	<0.001
EV71-positivity	366 (64.6)	84 (86.6)	<0.001
Death [#]	0 (0)	97 (14.6)	–

Notes: Values are n or n (%), unless otherwise noted. [#]Causes of death were acute pulmonary oedema, brainstem encephalitis and circulatory failure.

Abbreviations: HFMD, hand, foot, and mouth disease; EV71, enterovirus 71; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio.

months, which were divided into two groups as ≤3 years old (n=526, 79.2%) and 3–6 years old (n=138, 20.8%). Patients who survived (n=567, 85.4%) or died (n=97, 14.6%) of HFMD differed significantly in terms of age, peak temperature, central nervous symptoms, cardiopulmonary systems, fasting glucose (>8.3 mmol/L), current EV71 infection and NLR median (range) [1.92 (0.20, 19.35) vs 3.43 (0.62, 13.85), $P < 0.001$].

Based on Youden's analysis, the ROC curve and interactive dot diagram for calculating the optimal cutoff value of NLR in predicting mortality is shown in Figure 1. An NLR cutoff value of 2.01 was used to classify patients into groups with high NLR (NLR > 2.01) or low NLR (NLR ≤ 2.01). The high-NLR group showed

**Figure 1** ROC curve and interactive dot diagram for calculating optimal cutoff value of NLR in predicting mortality generated for 664 patients with critical HFMD.

significantly higher death risk than the low-NLR group ($P < 0.001$).

Univariate analysis of 664 patients (567 survived, 97 died) revealed significant differences ($P < 0.001$) in the frequency of fasting blood glucose >8.3 mmol/L, current EV71 infection, and NLR > 2.01. Multivariate analysis identified the following as independently associated with risk of death from severe HFMD (Table 2): high fever (>39.0 °C) (OR 3.342, 95% CI 1.736–6.432), EV71 infection (OR 3.200, 95% CI 1.529–6.698), fasting glucose

Table 2 Analysis of Potential Risk Factors for Severe HFMD

Risk Factors	Unadjusted OR	Adjusted [#]
Gender	1.112 (0.714–1.730)	1.131 (0.615–2.079)
Age	0.394 (0.199–0.781)**	0.557 (0.234–1.323)
High fever (> 39.0°C)	3.949 (2.330–6.694)***	3.342 (1.736–6.432)***
EV71-positivity	3.549 (1.930–6.524)***	3.200 (1.529–6.698)**
Fasting glucose > 8.3 mmol/L	49.014 (25.042–95.935)***	37.343 (18.616–74.909)***
NLR > 2.01	3.724 (2.252–6.157)***	2.142 (1.125–4.079) *

Notes: Values are OR (95% CI). [#]In multivariate logistic regression model (n = 664), we controlled for age, gender, High fever (> 39.0°C), EV71-seropositivity, fasting glucose and NLR > 2.01. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Abbreviations: EV71, enterovirus 71; NLR, neutrophil/lymphocyte ratio.

(OR 37.343, 95% CI 18.616–74.909), and NLR > 2.01 (OR 2.142, 95% CI 1.125–4.079).

Characteristics of Patients with Severe or Critical HFMD and Risk Factors for Mortality

The study involved 664 patients diagnosed with critical HFMD, including 137 with critical disease and 97 who died (Table 3). Patients who survived or died differed significantly in age, fasting glucose >8.3 mmol/L, EV71 infection and NLR median (range) [1.87 (0.25–14.08) vs 3.43 (0.62–13.85), $P < 0.001$].

The ROC curve and interactive dot diagram for calculating the optimal cutoff value of NLR in predicting mortality generated for 137 patients with critical HFMD is shown in Figure 2. An NLR cutoff value of 2.50 was

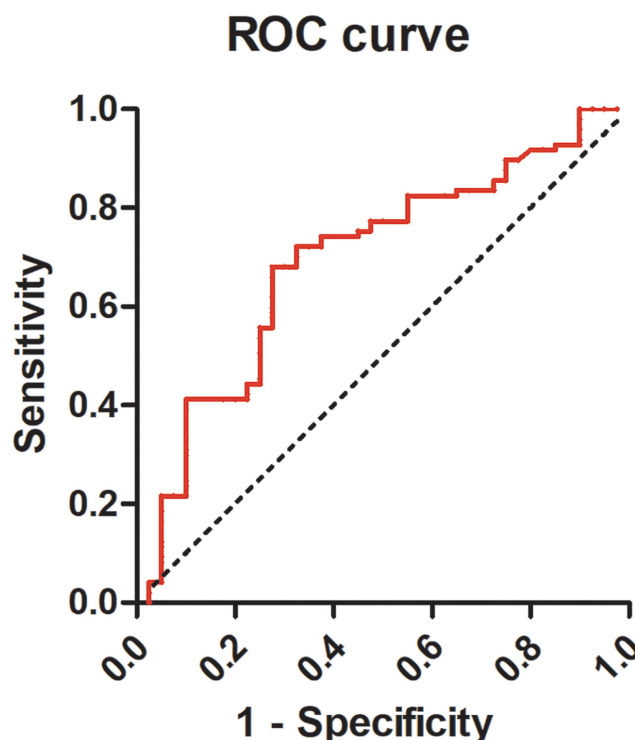


Figure 2 ROC curve and interactive dot diagram for calculating optimal cutoff value of NLR in predicting mortality generated for 137 patients with critical HFMD.

Table 3 Clinicodemographic Characteristics of Patients with Critical HFMD Who Died or Survived During the Study Period

Relevant Factors	Survived (n=40)	Died (n=97)	P
Male/female	27/13	59/38	0.462
Age, yr			0.027
≤3	30 (75.0)	87 (89.7)	
>3	10 (25.0)	10 (10.3)	
Rash	40 (100.0)	97 (100.0)	–
Fever	40 (100.0)	97 (100.0)	–
Duration of fever >3 d	34 (85.0)	72 (74.2)	0.171
Peak temperature (>39 °C)	30 (75.0)	78 (80.4)	0.481
Hypersomnia	40 (100.0)	91 (93.8)	–
Hyperarousal	39 (97.5)	91 (93.8)	0.290
Limb shaking	35 (87.5)	83 (85.6)	0.766
Convulsion	21 (53.8)	40 (41.2)	0.228
Vomiting	33 (82.5)	64 (66.0)	0.053
Pathologic reflexes	39 (97.5)	97 (100.0)	–
Dyspnoea	36 (90.0)	97 (100.0)	–
Circulatory disturbance	40 (100.0)	97 (100.0)	–
PCT (>0.20ng/mL)	27 (67.5)	49 (50.5)	0.07
NLR, median (range)	1.87 (0.25–14.08)	3.43 (0.62–13.85)	0.001
NLR, mean±SD	2.77 ± 2.70	4.17 ± 2.81	–
NLR (≤3 yr, n=117)	2.54 ± 2.08 (n=30)	3.91 ± 2.73 (n=87)	0.014
NLR (3–6 yr, n=20)	3.48 ± 4.11 (n=10)	6.46 ± 2.63 (n=10)	0.07
NLR > 2.50	13 (32.5)	66 (68.0)	<0.001
Fasting blood glucose level >8.3 mmol/L	14 (35.0)	86 (88.7)	<0.001
EV71-positivity	27 (67.5)	84 (86.6)	0.01

Note: Values shown are n or n (%), unless otherwise noted.

Abbreviations: HFMD, hand, foot, and mouth disease; EV71, enterovirus 71; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio.

used to classify patients into those with high NLR (NLR > 2.50) or low NLR (NLR ≤ 2.50). The high-NLR group was at significantly higher death risk than the low-NLR group ($P < 0.001$).

Risk factors for critical HFMD are summarised in Table 4. Univariate analysis of 40 surviving and 97 dead patients revealed significant differences ($P < 0.001$) in the incidence of fasting blood glucose > 8.3 mmol/L, current EV71 infection, and NLR > 2.50. The multivariate model of 137 critical cases identified the following factors associated with death risk: EV71 infection (OR 3.441, 95% CI 1.132–10.462), fasting glucose (OR 14.173, 95% CI

Table 4 Analysis of Risk Factors for Mortality Associated with Severe HFMD

Risk Factors	Unadjusted	Adjusted [#]
Gender	0.345 (0.131–0.909)*	0.587 (0.212–1.630)
Age	1.338 (0.615–2.910)	0.671 (0.170–2.650)
EV71-positivity	3.111 (1.287–7.520)*	3.441 (1.132–10.462)*
NLR > 2.50	4.422 (2.012–9.717)***	4.166 (1.570–11.051)*
Fasting glucose > 8.3 mmol/L	14.519 (5.883–35.832)***	14.173 (4.920–40.827)***

Notes: Values are OR (95% CI). [#]In multivariate logistic regression model (n = 137), we controlled for age, gender, EV71-seropositivity, fasting glucose and NLR > 2.50. * $P < 0.05$, *** $P < 0.001$.

Abbreviation: NLR, neutrophil/lymphocyte ratio.

4.920–40.827), and $\text{NLR} > 2.50$ (OR 4.166, 95% CI 1.570–11.051).

Discussion

In this retrospective study, we aimed to explore the correlation between NLR and risk of mortality in patients with severe HFMD. Multivariate analysis of data from 664 patients identified EV71 infection, WBC count, fasting glucose and $\text{NLR} > 2.01$ as independently associated with the risk of death from severe HFMD. Uni- and multivariate analyses identified current EV71 infection, fasting glucose and $\text{NLR} > 2.50$ as risk factors for mortality in patients with critical HFMD. Early detection of these risk factors and timely intervention are important to control mortality due to severe HFMD.

NLR is obtained by simply dividing the number/proportion of neutrophils by that of lymphocytes, so it can be calculated from the differential white cell count test routinely performed in most clinical settings. Thus it is a convenient marker of systemic inflammatory response. Our results add to the growing list of diseases where NLR may be clinically useful as a prognostic marker. Growing evidence suggests that NLR and other haematological markers of the systemic inflammatory response can reliably predict inflammatory response and survival in patients with malignancy.^{9–14} Many groups have investigated the prognostic value of the NLR in a variety of inflammatory diseases at differing stages of disease.^{16,17}

The relationship between increased NLR and poor prognosis is not fully understood in adults, and high NLR is thought to be indicative of inflammation. For example, proinflammatory cytokines in the plasma of patients with $\text{NLR} > 5$ may establish and maintain a tumour microenvironment favouring aggressive tumour behaviour. This may explain why elevated NLR appears to be associated with recurrence of hepatocellular carcinoma.¹⁸ In fact, NLR may show greater predictive power than the classical inflammatory marker C-reactive protein or total WBC count for discriminating patients with or without Crohn's disease.¹⁹

In children, NLR has already been associated with the activity of several infectious diseases. One study showed that the combination of NLR and C-reactive protein/mean platelet volume ratios may be useful for differential diagnosis of bacterial or viral pneumonia, as well as prediction of complications.¹³ NLR may be used as a diagnostic marker of febrile urinary tract infection,²⁰ and it may be elevated in multidrug-resistant *Pseudomonas aeruginosa*

infection in patients with hospital-acquired pneumonia.²¹ Our results in the present study lead us to suggest that NLR may be a useful inflammatory marker for predicting severity of HFMD and risk of associated mortality.

The early hyperdynamic phase of infection is mediated by neutrophils, macrophages and monocytes, with the release of inflammatory cytokines. Overexpression of inflammatory cytokines and chemokines can induce excessive immune responses and cause cytokine cascade reaction and cytokine storm in EV71-infected tissues.²² Severe HFMD involves the release of a large number of pro-inflammatory factors including interleukin (IL)-6, IL-12, IL-18, tumour necrosis factor- α , and interferon- γ .²² This release of proinflammatory cytokines and acute-phase factors can increase WBC count. During the systemic inflammatory response, neutrophil apoptosis is suppressed and lymphocyte apoptosis is promoted.²³ Thus, NLR may be a particularly useful index because it reflects inflammatory processes (neutrophils) as well as immunoregulatory processes (lymphocytes). We speculate that the increase in NLR in HFMD is caused by cytokine-mediated recruitment of neutrophils. During HFMD progression, various cytokines and chemokines likely contribute to inflammation and may be valuable for monitoring progression and predicting prognosis. This inflammation may then help explain why increased NLR is associated with mortality risk in patients with severe HFMD.

In this large cohort of infants and young children not older than 6 years, we found that $\text{NLR} > 2.50$ can predict mortality of severe HFMD. To the best of our knowledge, this is the first study to assess NLR as a diagnostic marker of severe HFMD in such a young population. NLR appears to correlate positively with age at least in healthy individuals,²⁴ and neutrophil and lymphocyte counts change significantly from birth to young adulthood,¹² and we verified that there were statistically significant differences in NLR values between different age groups (≤ 3 yr vs 3–6 yr, 2.67 ± 2.36 vs 3.83 ± 3.00 , $P < 0.001$) in this study. Despite the effect of age on NLR, age-independent NLR was associated with the prognosis of HFMD patients (Tables 1 and 3). Thus, appropriate NLR cutoff values for classifying patients as low or high will depend on age. Previous work with healthy children younger than 20 years (mean age, 16 years) indicated a mean NLR value of 1.53 ± 0.56 .²⁴ In contrast, an NLR cutoff > 5 has been suggested for detecting bacteraemia or sepsis in adults.²⁵

Our study also found that EV71 infection and high fasting glucose were associated with increased risk of

death from severe HFMD. Similar findings were reported in other studies.^{26,27} In recent years, EV71 has caused large-scale outbreaks of HFMD and substantial child mortality in the Asia-Pacific region.^{28,29} Now, vaccines against EV71 have become available in some Asian countries, such as in China.^{30–34} However, there are still a few challenges facing the worldwide use of EV71 vaccine.³⁵ So, adequate prevention of severe cases of HFMD and determining factors that predict HFMD severity are very most important to make better clinical decisions.

A few limitations of this study are worth considering. The study was relatively small and involved patients from only two medical centres. In addition, the study was retrospective, increasing the risk of selection and analytical bias, and NLR was not observed over time. These factors make it impossible to establish causal relationships between NLR and all-cause mortality. It will be important in future work to see whether NLR increases as patient condition progressively deteriorates; in parallel, levels of various cytokines should be assayed. Our results justify further work to clarify how high NLR may contribute to severe HFMD.

Conclusions

The NLR can be easily calculated from routine differential neutrophil and lymphocyte counts, making it more straightforward and less expensive than many other inflammatory markers. NLR may be able to predict risk of HFMD-associated mortality, providing additional stratification beyond conventional risk scores.

Ethical Approval and Informed Consent

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University and Xi'an Children's Hospital. Informed consent was not required for a retrospective study.

Acknowledgments

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Disclosure

The authors declare that they have no conflicts of interest.

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