Original Article

Decreased Prognostic Value of International Prognostic Score in Chinese Advanced Hodgkin Lymphoma Patients Treated in the Contemporary Era

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Abstract

Background: The International Prognostic Score (IPS) was developed based on the data of Western advanced Hodgkin lymphoma (HL) patients treated before 1992. Only a few studies ever evaluated the application value of IPS in Chinese population or in patients treated in the contemporary era whose outcomes has improved significantly than before.

Methods: We conducted a retrospective study involving 208 previously untreated Chinese advanced HL patients, who were admitted to Cancer Hospital Chinese Academy of Medical Sciences from January 1, 1999 to April 30, 2015 and received uniform first-line treatment. The prognostic value of both IPS and the seven IPS factors for freedom-from progression (FFP) and overall survival (OS) was assessed in this population. The statistical methods included Kaplan-Meier methodology, log-rank testing, and Cox proportional hazard regression analysis.

Results: With a median follow-up time of 79 months (range, 15–210 months), the 5-year FFP and OS were 78.8% and 86.0% respectively, which improved obviously compared with the original IPS study. The IPS remained prognostic for both FFP ($P = 0.041$) and OS ($P = 0.013$), but the range narrowed obviously, with 5-year FFP ranging from 87.2% to 61.5%, 5-year OS ranging from 94.1% to 69.2%, and the separation of survival curves was not as good as before. Only two of the seven IPS factors showed a significant independent prognostic value in the multivariate analysis: Stage IV (for FFP, hazard ratio [*HR*] = 2.219, 95% confidence interval [*CI*]: 1.148–3.948, $P = 0.016$; for OS, *HR* = 2.491, 95% *CI*: 1.159–5.355, $P = 0.019$) and hemoglobin <105 g/L (for FFP, *HR* = 2.136, 95% *CI*: 1.123–4.060, $P = 0.021$; for OS, *HR* = 2.345, 95% *CI*: 1.099–5.042, $P = 0.028$). A simple prognostic score calculated by adding one point each for any of the two factors was prognostic both for FFP ($P < 0.001$) and OS ($P < 0.001$) with the survival curves separating very well, but the range still narrowed.

Conclusions: The IPS has decreased the prognostic value in Chinese advanced HL patients treated in the contemporary era. More prognostic factors are needed to supplement this original scoring system so as to identify different risk populations more accurately.

Key words: Hodgkin Lymphoma; International Prognostic Score; Prognosis

Introduction

Hodgkin lymphoma (HL) accounts for about 10% of lymphomas in China.[1] It is a curable disease, but about 30% of advanced HL patients will suffer relapse, and some lower risk patients may be overtreated, resulting in increased toxicity during the long-term survival.[2,3] It is highly important to identify advanced HL patients with different prognoses accurately, according to which a more appropriate therapy scheme could be made for individuals to increase the cure rate of patients with high risk and avoid possible overtreatment in patients with lower risk.

The International Prognostic Score (IPS) was a 7-factor score system developed based on the data of more than

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5000 patients with advanced HL in 1998, which predicts 5-year freedom-from progression (FFP) ranging from 42% to 84% with each additional factor reducing survival rate by 8% and predicts 5-year overall survival (OS) from 56% to 89%.[4] IPS was widely used to guide the choice of individualized risk-adapted therapy since 1998. However, all the 5000 patients were treated before 1992. With the medical technology progressing rapidly over the past decades, especially more effective treatment regimens and the enhanced supportive care, patients' outcomes have improved obviously than before,[5-8] and the application value of IPS may change. The National Comprehensive Cancer Network-International Prognostic Index for diffuse large B-cell lymphoma (DLBCL) could be a good example for our deduction, which has stronger prognostic value compared with original IPI for patients treated in the rituximab era who have an ameliorated outcome.[9,10] Furthermore, all the 5000 patients in the original IPS study were from western countries. Whether IPS applies to Chinese people remains to be explored.

We carried out this retrospective study to assess the predictive value of IPS for survival in Chinese advanced HL patients treated in the contemporary era.

Methods

Patients

Of all the advanced HL patients consecutively admitted to Cancer Hospital Chinese Academy of Medical Sciences (CHCAMS) from January 1, 1999 to April 30, 2015, 208 individuals were included in this study, who met the following inclusion criteria of this study: histologic and imaging confirmation of advanced HL (defined as Stage III/IV or Stage I/II with bulky disease) with an age range of 15–67 years, previously untreated, no previous history of malignancy, combination chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine [ABVD]) with or without radiotherapy (applied to bulky tumors or to the sites of residual disease) as the first-line treatment, clinical data were complete and available from the hospital medical records. The exclusion criteria were as follows: severe cardiopulmonary or hepatic or renal dysfunction, pregnancy, immunosuppression, immunodeficiency, immunosuppressive medication users, history of transplantation. We obtained all the required information from the case management system in the medical record room of CHCAMS. This study was in compliance with the *Declaration of Helsinki* and was approved by the Medical Ethics Committee of CHCAMS. As this is a retrospective study, the informed consent was exempted. Patient records were anonymized and de-identified prior to the analysis.

Patients' baseline clinical and laboratory parameters were collected, especially seven IPS factors. The frequency of follow-up back to hospital after treatment was as follows: every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually or whenever clinically indicated after 5 years. FFP was defined as the interval from the date of diagnosis to the first recurrence (progression or relapse) of disease or the date of last follow-up in patients with no relapse; deaths not caused by disease progression/relapse during remission or loss to follow-up were censored. OS is defined as the interval from the date of diagnosis to the death from any cause or the date of last follow-up with loss to follow-up censored. There were various treatment regimens in progressed or recurrent cases, and salvage therapy could rescue many relapsed patients, so the prognostic value of IPS for FFP was regarded as the primary end point.

Statistical analysis

FFP and OS were calculated with Kaplan-Meier methodology and compared between groups using log-rank testing. Estimates of the predictive effect of seven IPS factors for FFP and OS were expressed as hazard ratios (*HR*s) in univariate and multivariate Cox proportional hazard regression analyses with a 95% confidence interval (*CI*). $P < 0.05$ was considered to be statistically significant. The statistical analyses were performed using SPSS version 22.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The baseline characteristics of patients are shown in Table 1. The median age was 36 years (range, 15–67 years), and 46 cases (22.1%) were more than 45 years. About half of the patients (47.6%) were male and 86 cases (41.3%) had Stage IV disease. The two most common pathological types were nodular sclerosis classical HL (48.6%) and mixed cellularity classical HL (33.7%). Less than half of the cases (41.8%) received chemoradiotherapy as the first-line treatment. The three hematological indexes of IPS were present in no more than 20% of the patients. The IPS score of all the patients was also collected. We considered patients with IPS ≥5 as a group for only three patients had a score ≥6. The patient characteristics of the original IPS study are also shown in Table 1 for comparison.[4]

At a median follow-up of 79 months (range, 15–210 months), 47 patients progressed or relapsed and 32 patients died. Twenty-eight died of HL; one died from pneumonia; one died of cardiac disease; and two died due to second primary malignancy. One patient was lost to follow-up. The 5-year FFP and 5-year OS were 78.8% and 86.0% respectively, which improved significantly compared with the original IPS study (66% and 78% respectively).[4]

Predictive value of International Prognostic Score

The IPS remained prognostic for both FFP ($P = 0.041$) [Figure 1a] and OS ($P = 0.013$) [Figure 1b] of the 208 patients, but the predictive magnitude narrowed obviously, with 5-year FFP ranging from 87.2% (score = 0) to 61.5% (score ≥5) and 5-year OS ranging from 94.1% (score = 0) to 69.2% (score ≥5) whereas the 5-year

Table 1: Baseline patient characteristics of the present study and the original IPS study

Characteristics	Present study	Original IPS study
Age (years), median (range)	36 (15–67)	NR (15–65)
Stage, *n*/*N* (%)		
I or II	29/208 (13.9)	603/4692 (13)
III	93/208 (44.7)	2110/4692 (45)
IV	86/208 (41.3)	1992/4692 (42)
B symptoms, *n*/*N* (%)	102/208 (49.0)	3274/4582 (71)
Histopathology, *n*/*N* (%)		
NSCHL	101/208 (48.6)	2936/4692 (63)
MCCHL	70/208 (33.7)	1202/4692 (26)
LRCHL	10/208 (4.8)	162/4692 (3)
LDCHL	5/208 (2.4)	124/4692 (3)
NLPHL	6/208 (2.9)	NR
Unclassified HL	16/208 (7.7)	268/4692 (6)
Bulky disease, *n*/*N* (%)	47/208 (22.6)	768/3436 (22)
Primary treatment, *n*/*N* (%)		
Chemotherapy	121/208 (58.2)	NR
Chemoradiotherapy	87/208 (41.8)	NR
IPS risk factors, *n*/*N* (%)		
Male	99/208 (47.6)	2882/4693 (61)
Age ≥45 years	46/208 (22.1)	991/4695 (21)
Stage IV	86/208 (41.3)	1979/4692 (42)
Serum albumin <40 g/L	122/208 (58.7)	1457/4314 (64)
Hemoglobin <105 g/L	40/208 (19.2)	NR
WBC ≥15×10^9/L	41/208 (19.7)	NR
Lymphocyte <0.6×10^9/L or <8% of WBC	31/208 (14.9)	NR
IPS, *n*/*N* (%)		
0	21/208 (10.1)	115/1618 (7)
1	48/208 (23.1)	360/1618 (22)
2	61/208 (29.3)	464/1618 (29)
3	41/208 (19.7)	378/1618 (23)
4	24/208 (11.5)	190/1618 (12)
≥5	13/208 (6.3)	111/1618 (7)

HL: Hodgkin lymphoma; NSCHL: Nodular sclerosis classical Hodgkin's lymphoma; MCCHL: Mixed cellularity classical Hodgkin's lymphoma; LRCHL: Lymphocyte-rich classical Hodgkin's lymphoma; LDCHL: Lymphocyte-depleted classical Hodgkin's lymphoma; NLPHL: Nodular lymphocyte-predominant Hodgkin's lymphoma; IPS: International Prognostic Score; NR: Not reported; WBC: White blood cell.

FFP ranged from 84% to 42% and the 5-year OS ranged from 89% to 56% in the original IPS study. The separation of survival curves was not as good as the original IPS study,[4] even the 5-year FFP of score 1 was lower than score 0 (85.2% vs. 87.2%), and the OS curves of the different groups overlapped with each other.

Prognostic significance of individual International Prognostic Score factors

The IPS include seven parameters (male, age ≥45 years, Stage IV, hemoglobin <105 g/L, white blood cell [WBC] >15 × 10^9/L, lymphocyte count <0.6 × 10^9/L or 8% of WBC, and albumin <40 g/L). The prognostic significance of individual IPS factors for FFP and OS evaluated by the Cox proportional hazard regression analysis is shown in Table 2. In univariate analysis, only stage (P = 0.002) and hemoglobin (P = 0.001) were prognostic for FFP. Apart from stage (P = 0.002) and albumin (P = 0.001), age (P = 0.025) was also associated with unfavorable OS significantly in univariate analysis. Multivariate analysis shows that stage and hemoglobin have significant independent negative prognostic value both for FFP (*HR* = 2.219, 95% *CI*: 1.148–3.948, P = 0.016; *HR* = 2.136, 95% *CI*: 1.123–4.060, P = 0.021) and OS (*HR* = 2.491, 95% *CI*: 1.159–5.355, P = 0.019; *HR* = 2.345, 95% *CI*: 1.099–5.042, P = 0.028).

A simple prognostic score

A simple prognostic score developed with stage and hemoglobin was calculated by adding one point each for any of the two factors (score range, 0–2). Figure 2a and 2b illustrated the survival curves of different scores and the corresponding number of patients together with the 5-year FFP and 5-year OS. This simple prognostic score was prognostic both for FFP (P < 0.001) and OS (P < 0.001). For each pair of adjacent scores, the FFP and OS were significantly different (FFP: score 0 vs. score 1, P = 0.033, score 1 vs. score 2, P < 0.001; OS: score 0 vs. score 1, P = 0.040, score 1 vs. score 2, P < 0.001), and the separation of survival curves was quite good. However, the predicted range still narrowed obviously, with 5-year FFP ranging from 85.9% to 58.2% and 5-year OS ranging from 91.5% to 68.8%.

Discussion

This study showed that IPS has decreased prognostic discrimination in Chinese advanced HL patients treated in the contemporary era, whose outcomes improved obviously compared with patients in the original IPS study. Of the seven IPS factors, only stage and hemoglobin remain independent prognostic values for survival.

Our findings were consistent with the study conducted by British Columbia Cancer Agency (BCCA),[11] where the prognostic value of IPS for advanced HL was assessed in British patients treated between 1980 and 2010. The IPS remained prognostic for FFP and OS in patients under 65 years in BCCA study with a narrowed 5-year FFP ranging from 88% to 70% and a narrowed 5-year OS ranging from 98% to 73%. Similarly, a retrospective analysis of data in the clinical trial E2496 that enrolled advanced HL patients from different western countries also reported an improved outcome and a decreased utility of IPS.[12] The 5-year FFP ranged from 83% to 68% and 5-year FFP from 98% to 74% in E2496 study with survival curves of different IPS scores overlapping with each other. We have a smaller sample size but the patients' first-line treatment regimens are uniform in our study, while individuals in BCCA and E2496 study were treated with different regimens. These three studies were conducted in different countries, so we inferred that ethnicity has no effect on the deceased utility of IPS.

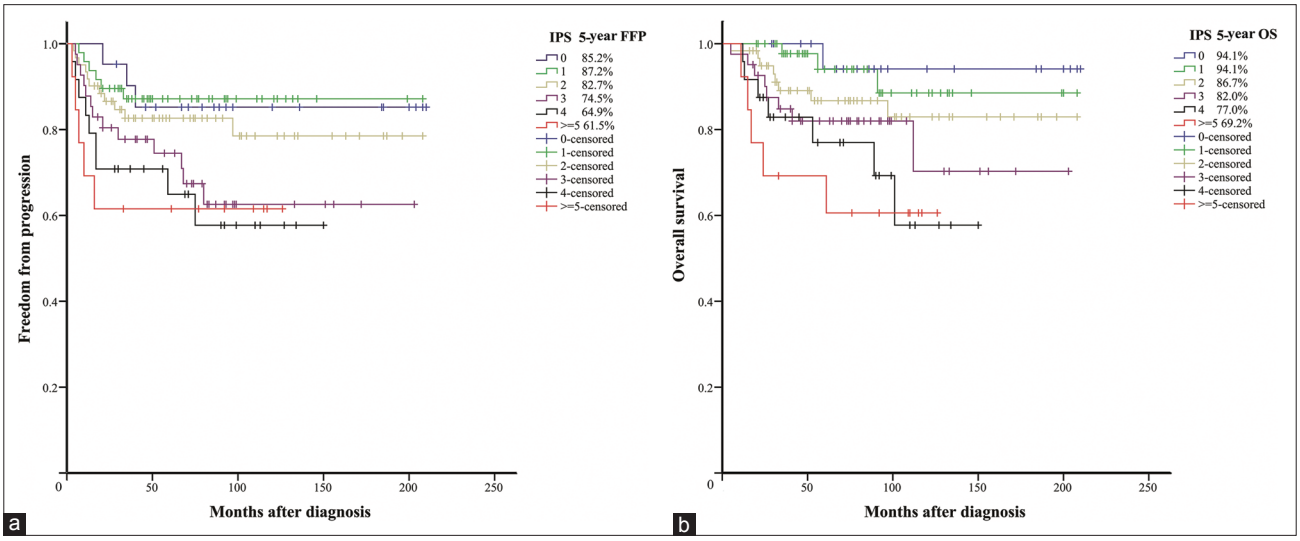

Figure 1: FFP and OS according to the IPS. (a) FFP. (b) OS. FFP: Freedom-from progression; OS: Overall survival; IPS: International Prognostic Score.

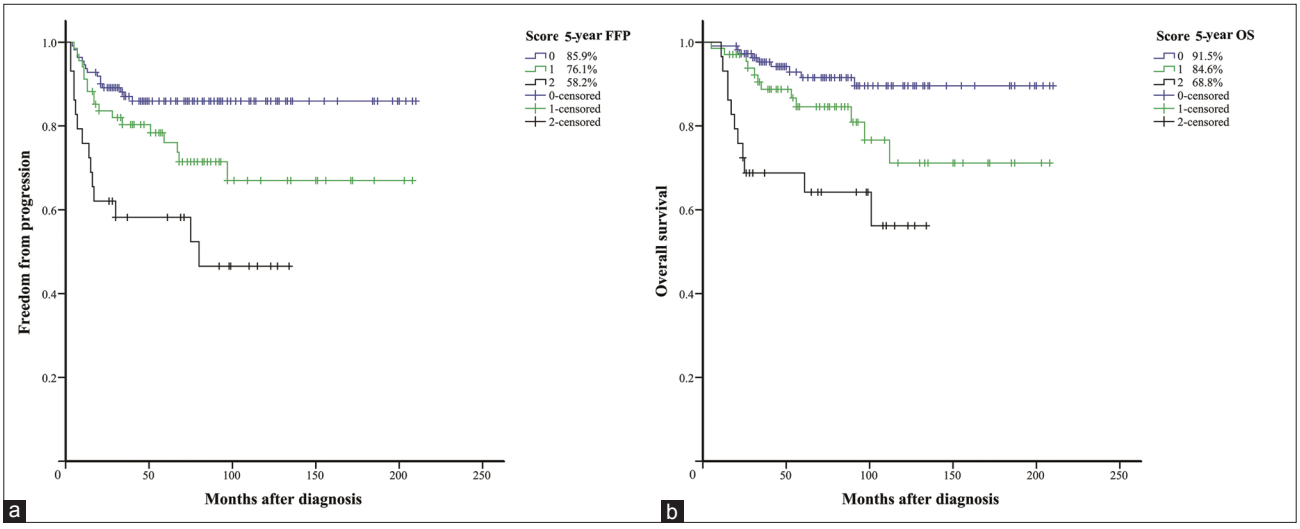

Figure 2: FFP and OS according to the simple prognostic score. (a) FFP. (b) OS. FFP: Freedom-from progression; OS: Overall survival.

Table 2: Univariate and multivariate analysis of seven IPS factors for FFP and OS

IPS factors	FFP				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Male	1.289 (0.711–2.338)	0.403	1.259 (0.686–2.308)	0.457	1.165 (0.569–2.384)	0.676	1.010 (0.487–2.095)	0.979
Stage IV	2.561 (1.422–4.613)	0.002	2.129 (1.148–3.948)	0.016	3.519 (1.521–6.558)	0.002	2.491 (1.159–5.355)	0.019
Age ≥45 years	1.604 (0.858–2.988)	0.139	1.321 (0.713–2.651)	0.415	2.267 (1.108–4.639)	0.025	1.968 (0.922–4.201)	0.080
Hemoglobin <105 g/L	2.787 (1.537–5.055)	0.001	2.136 (1.123–4.060)	0.021	3.209 (1.583–6.503)	0.001	2.345 (1.099–5.042)	0.028
WBC ≥15×10^9/L	1.292 (0.657–2.540)	0.457	1.137 (0.558–2.320)	0.724	1.386 (0.622–3.091)	0.425	1.061 (0456–2.465)	0.891
Lymphocyte <0.6×10^9/L or <8% of WBC	1.657 (0.824–3.332)	0.157	1.219 (0.586–2.536	0.596	1.677 (0.725–3.879)	0.227	1.213 (0.497–2.963)	0.671
Serum albumin <40 g/L	1.068 (0.596–1.913)	0.824	1.436 (0.770–2.680)	0.255	1.081 (0.535–2.194)	0.825	1.714 (0.788–3.728)	0.174

IPS: International Prognostic Score; FFP: Freedom-from progression; OS: Overall survival; *HR*: Hazard ratio; *CI*: Confidence interval; WBC: White blood cell.

IPS was developed based on the data of patients treated before 1992.[4] Patient outcomes in the modern era have improved obviously than before. It was reflected in many studies[5-8] apart from the two studies mentioned above, and was further proved in our study, which was thought to be the major cause for the decreased utility of IPS. Besides the Revised International Prognostic Index for DLBCL, Follicular Lymphoma International Prognostic Index-2[13] could be taken as another sample, which was developed based on the data of patients treated in the era of rituximab-containing chemoimmunotherapy regimens who have an improved survival compared with those in the era of chemotherapy alone. There are many reasons contributing to the improvement of advanced HL. First, more accurate pathologic diagnosis has identified patients with non-HL previously mistaken for HL[14] or patients with HL previously mistaken for other diseases.[15] Second, ABVD has been widely used in clinical practice as a more effective treatment regimen over mechlorethamine, Oncovin (vincristine), procarbazine, and prednisone.[5] Continuously improved autologous bone marrow transplantation technique has prolonged survival as well.[16,17] Third, improved toxicity management methods such as neutrophil growth factors guaranteed the chemotherapeutics dose intensity, which is crucial for optimizing efficacy.[18] Next, new generation of imaging techniques has identified some advanced disease previously mistaken for limited disease.[19] Finally, enhanced supportive care has prolonged patients' survival as well.

Stage IV is one of the independent prognostic factors both for FFP and OS in our study. While in BCCA study, Stage IV was not prognostic for OS.[11] It is worth noting that patients with Stage IV disease in BCCA study only comprised 24% of the patient population, compared to 41% and 42% in our study and the original IPS study, respectively, so patients of Stage IV are not well represented in BCCA study. Hemoglobin <105 g/L is another negative prognostic factor we revealed, which also showed a significant prognostic effect in BCCA ($P < 0.001$ for FFP and $P < 0.001$ for OS) and E2496 study ($P = 0.004$ for FFP and $P = 0.002$ for OS).[11,12] Anemia could cause decreased capacity of oxygen transport and thus lead to tumor hypoxia, which could result in the resistance of cancer cells to radiotherapy or chemotherapy.[20] Anemia has been proved to be negatively correlated with the survival of many other malignancies.[21] Age ≥45 years had no independent significant prognostic value in our study, but it was prognostic for survival in BCCA study (for FFP, $P = 0.031$; for OS, $P = 0.042$). A key point here is that all patients enrolled in our study were under 67 years as older patients were usually given with an inadequate dose or recommended to the general hospital to receive better supportive care, while in BCCA study, all the patients aged 16–85 years were analyzed.[11] So was the E2496 study,[12] in which patients of any age were included and age showed independent prognostic significance for OS ($P < 0.001$). We had a patients' cohort with a narrower age range (15–67 years), but it coincides with the age range of patients in the original IPS study (15–65 years).[4] Furthermore, some investigators suggested that the prognosis of elderly HL should be analyzed separately since they found this special population had a disproportionately inferior survival compared with younger patients due to poor tolerance to the treatment.[22,23] A study enrolled 95 elderly HL patients treated from 1999 to 2009 and found that this population had a 5-year PFS of 44% and a 5-year OS of 58% with age >70 years being an independent prognostic factor.[24]

Other factors of IPS showed no independent prognostic significance in these three studies, but nobody could make an absolute judgment for the relatively small sample sizes compared with the sample of 5000 in the original IPS study.

In our study, a simple prognostic score calculated by adding 1 point each for any of the two parameters identified FFP and OS accurately and relatively, but the predicted range still narrowed. More prognostic parameters are needed to supplement and perfect the scoring system. In the past several years, there has been a marked tendency to search for new, more specific and sensitive prognostic factors in HL. For example, tumor-associated macrophages, lymphocyte/monocyte ratio, EBV expression, and early PET scanning have been proved to be correlated with a poorer prognosis of HL.[25-30]

It should be noted that this study has limitations. We carried out a totally retrospective analysis with a relatively low patient number. A multicenter study with larger group of patients from different institutions or areas in China is needed to evaluate the prognostic value of IPS and individual IPS factors for Chinese advanced HL patients treated in the contemporary era.

In conclusion, the prognostic value of IPS in Chinese advanced HL patients treated in the contemporary era has decreased. More prognostic factors are needed to supplement this original scoring system so as to identify different risk populations more accurately.

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Conflicts of interest

There are no conflicts of interest.

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