CLINICOPATHOLOGIC CHARACTERISTICS AND ITS ASSOCIATION WITH SURVIVAL OUTCOMES IN GASTRIC CANCER AFTER D2 RESECTION FOLLOWED BY S1 AND OXALIPLATIN AS ADJUVANT THERAPY

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There is limited data about the clinic-pathological features and the predictors of survival in gastric cancer patients who received adjuvant SOX post-operation in Vietnam. This study aimed to identify the correlation between clinic-pathological features and clinical outcomes for this population. From January 2019 to December 2023, 69 patients aged above 18 years old were diagnosed with gastric cancer and treated at the National Cancer Hospital Vietnam. Clinical findings, histo-pathological parameters and outcomes were reviewed retrospectively. Clinic-pathological characteristics of the study population showed a predominance of males (60.8%), aged above 60 (52.17%), good performance status, undifferentiated tumour (68.12%), antrum cancers (86.96%), and lymph nodes involvement (75.36 %). The estimated 1-year, 2-year, 3-year overall survival (OS) and disease free survival (DFS) were 92.6%, 77.7%, 74.9% and 80.9%, 72.5% and 72.5%, respectively with the median follow-up period of 17 months. A significant prognostic predictor for survival was the presence of lymph node invasion (p = 0.0167) in a univariate analysis. Gastric cancer patients with adverse prognostic factors (node-positive) have a poor prognoses. Adjuvant chemotherapy may be more beneficial for these patients.

Keywords: Gastric cancer, prognosis, adjuvant SOX.

I. INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies in the world and is the second leading cause of cancer-related death worldwide.[1] Although GC incidence has steadily decreased over recent decades and early detection with following treatment has progressed, it remains as a major clinical challenge.[2] Optimal treatment modalities for GC include endoscopic resection depending on tumour stage or surgery followed by adjuvant therapies. However, even with a potentially curative resection, approximately 50% of patients develop recurrence within 5 years after surgery, and 50% - 90% of patients die of tumour relapses.[3-5] In Vietnam, due to a lack of the national screening program for gastric cancer, most patients come to medical facilities in the advanced stage and under the circumstances, surgical resection with lymph node dissection followed by adjuvant chemotherapy or chemoradiation therapy may offer the best chance for long-term survival.[3,4] In recent years, adjuvant chemotherapy has been widely used for advanced gastric cancer patients to improve the 5-year overall survival rate. The ACTS-GC study, a randomized phase III trial, showed that the overall survival rate at 5 years was 71.7% in the adjuvant group and

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Received: 22/05/2024

Accepted: 13/06/2024

61.1% in the surgery-only group (HR = 0.669 [95%CI: 0.540 - 0.828]).[6] Another famous study in Asia, the CLASSIC study, also reported a hazard ratio for 5-year overall survival of 0.66 (95% CI: 0.51 - 0.85; p = 0.0015) for surgery and adjuvant chemotherapy with capecitabine and oxaliplatin for 6 months after a median follow-up of 62.4 months.[7] These results from randomized controlled trials provided hard evidence of the survival benefits associated with adjuvant chemotherapy.

Although, these adjuvant treatments have been largely approved in some Asian countries including Japan, Korea and China, there are limited data to present in the Southeast Asia region. To best our knowledge, in Vietnam, there are currently no reported study that evaluated GC in patients with adjuvant SOX chemotherapy. Similarly, little is known regarding predictors of GC survival for those who underwent resection followed by adjuvant SOX chemotherapy. Therefore, we conducted this research with the aim to *define the contemporary clinic-pathological characteristics and associated prognoses for this group of cancer patients*.

II. MATERIALS AND METHODS

1. Subjects

Between January 2019 and December 2023, 69 patients with GC stage II-III were treated at our hospital. The objective was to evaluate the correlation between clinic-pathological features and outcomes (OS and DFS) of SOX therapy as an adjuvant therapy in stage II - III gastric cancer patients who had undergone curative resection.

The inclusion criteria

- Histologically confirmed stage II-III gastric adenocarcinoma (according to the 8th edition of the American Joint Committee on Cancer tumour-node-metastasis system).

- R0 surgery with D2 or more extensive lymphadenectomy.

- Start chemotherapy within 8 weeks after surgery.

- No prior chemotherapy or radiotherapy.

- Sufficient oral intake.

- Age distribution of above 18 years old.

- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 1.

- Adequate bone marrow, renal and liver function, including an absolute granulocyte counts of > 1500/L; a platelet counts of > 100,000/L; a haemoglobin level of > 90 g/L; a serum bilirubin level of less than the upper limit of normal (ULN); a normal creatinine level; an alanine transaminase and aspartate transaminase level of < 1.5 × ULN.

- Electrocardiogram was normal.

The exclusion criteria

Patients with ascites or evidence of peritoneal, hepatic or distant metastases.

Mental abnormalities, severe comorbid conditions, severe drug hypersensitivity or peripheral sensory neuropathy.

Methods

Study design

This is a single-arm, single centre, retrospective, phase 2 study.

Location and duration

National Cancer Hospital Vietnam (Hanoi, Vietnam).

Between January 2019 and December 2023.

Study sample size

Convenience sampling: took all eligible patients into the study.

During the subject selection process, 69 patients were found to be eligible to participate in our study.

Treatment and assessment

Chemotherapy consisted of at least one cycle

and up to eight cycles of S1 plus oxaliplatin. All treatment cycles were administered every 3 weeks. S1 was administered orally twice daily at a dose of 80, 100 and 120 mg/day based on the body surface area of < 1.25, 1.25 - 1.5 and > 1.5m^2, respectively from day 1 to 14. Oxaliplatin was infused intravenously for 2 h on day 1 at a dose of 130 mg/m^2. Before infusion of oxaliplatin, anti-emetics (e.g., a 5-hydroxytryptamine3 receptor antagonist and dexamethasone) were administered prophylactically to prevent nausea and vomiting. If patients developed grade 3 - 4 haematological toxicities, or grade 3 - 4 diarrhea, laryngeal mucositis, peripheral sensory neuropathy and palmer-planter erythrodysestheia syndrome, the doses of both oxaliplatin and S1 were reduced by 15 - 25%. The dose of oxaliplatin was reduced if the platelet count was less than 75,000/mm^3 on day 23 with delayed initiation of the next treatment cycle or if grade 2 peripheral sensory neuropathy was noted on the first day of the next cycle. In the cases of oxaliplatin-related peripheral sensory neuropathy, S1 could be continued as monotherapy. But oxaliplatin monotherapy was not allowed if S1 was discontinued.

During the study, complete blood count and blood chemistry studies were performed before initiation of each cycle. Computed tomography, magnetic resonance image or abdominal ultrasound were performed as baseline before chemotherapy. Then, the presence or absence of disease recurrence was evaluated every 3 months for 2 years, then every 6 months for 3 years. Adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria version 4.0.

Statistical analysis

Baseline continuous and categorical variables are presented as the median with interquartile range (IQR) and number with percentage, respectively. Correlations between various factors and overall survival by GC were assessed by univariate and multivariate Cox proportional hazards regression analysis. Variables that were deemed of potential importance to the univariate analysis ($P < 0.05$) were included in the multivariate analysis. All P values were two-sided, and P values < 0.05 were considered to be statistically significant. Results for significant prognostic factors were expressed as the hazard ratio for each category and its 95% confidence interval. Patient survival (OS and DFS) was estimated using the Kaplan - Meier method. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc).

3. Research ethics

This study was launched in accordance with the Helsinki Declaration and the good clinical practice guidelines. All patients provided written informed consent before starting of the study.

III. RESULTS

Table 1 summarizes the patient overall clinical and histo-pathologic features. Among the 69 patients in our present study cohort, the median age was 61 years (IQR 27 - 81 years) with age group of above 60 account for 52.17%. The majority of patients were male (60.8%) and 41 patients (59.42%) had a very good performance status of 0.

With regard to histologic classification, the predominance of undifferentiated tumours (n = 47, 68.12%) was remarkable while differentiated tumours including high and moderate differentiation accounted for 7.25% and 15.94%, respectively.

The distribution of pathologic stages after surgery was as follows: stage IIA, n = 20 (29.34%); stage IIB, n = 8 (11.59%); stage IIIA, n = 18 (26.09%); IIIB, n = 12 (17.39%) and

stage IIIC, n = 11 (15.94%).

Concerning the depth of tumour invasion, 2 (2.90%) and 13 (18.84%) patients were diagnosed at T1 and T2 stage while most patients (n = 54, 78.26%) had stage of T3 and T4. Similarly, lymph node involvement (n = 52, 75.36%) was more common than node negative (n = 17, 24.64%).

Fifty-three patients (76.81%) completed eight cycles of treatment. Sixteen patients (23.19%) could not complete the eight cycles of treatment and the reason for discontinuation were as follows: two patients early discontinued therapy because of adverse events (fatigue and malnutrition after total gastrectomy), five patients were detected metastasis and others postponed adjuvant chemotherapy for long-lasting thrombocytopenia. Notably, one patient underwent re-surgery for bowel obstruction during treatment.

The median relative dose intensities in our study were 98.68% for S1 and 93.02% for oxaliplatin. Sixteen patients (16.7%) experienced one level of S1 dose reduction, and no patient required two level of S1 dose reduction. Forty-five patients (65.22%) experienced one level of oxaliplatin dose reduction, and eight patient (11.59%) required two level of dose reduction and experienced treatment delay of initiation subsequent cycle. The main reason of dose reduction and treatment delay were drug toxicities including thrombocytopenia, fatigue, diarrhea and peripheral sensory neuropathy.

Table 1. Patients' clinicopathological characteristics

Variable	Total (n = 69)	Variable	Total (n = 69)
Age (years)		*Tumour position*	
n	69	Unknown	1 (1.45%)
Mean ± SD	58.2 ± 9.85	Antrum	60 (86.96%)
Median	61.0	Pylorus	2 (2.90%)
Minimum - Maximum	27.0 - 81.0	Cardia	2 (2.90%)
Age group		Spread	4 (5.80%)
Equal and below 60	33 (47.83%)	*Tumour invasion*	
Above 60	36 (52.17%)	Mucosa and submucosa (T1)	2 (2.90%)
Gender		Musculature (T2)	13 (18.84%)
Male	42 (60.87%)	Serosa (T3)	18 (26.09%)
Female	27 (39.13%)	Subserosa (T4)	36 (52.17%)
ECOG		*Node involvement*	
0	42 (60.87%)	0	17 (24.64%)
1	27 (39.13%)	1 - 2	16 (23.18%)
Pathologic stage		3 - 6	21 (30.44%)
IIIa	18 (26.09%)	7 - 15	12 (17.40%)
IIIb	12 (17.39%)	≥ 16	3 (4.35%)

Variable	Total (n = 69)	Variable	Total (n = 69)
IIIc	11 (15.94%)	*Number of chemotherapy cycles*	
IIa	20 (29.34%)	1	1 (1.45%)
IIb	8 (11.59%)	2	1 (1.45%)
Histopathologic findings		5	2 (2.90%)
High differentiation	5 (7.25%)	6	6 (8.70%)
Moderate differentiation	11 (15.94%)	7	6 (8.70%)
Low differentiation	47 (68.12%)	8	53 (76.81%)
Unknown	6 (8.70%)	*Median relative dose intensities*	
		Oxaliplatin (%)	93.02
		S1 (%)	98.68

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SD, standard deviation

The outcomes of patients were shown in Figure 1 and Figure 2 below. The median follow-up period in our study was 17.0 (19.6 ± 12.55) months (IQR 2.0 - 51.0 months). At the interim analysis, there were twenty patients recurred. The 1-year estimated disease free survival were 80.9%, 2-year and 3-year DFS was 72.5% and 72.5%. On the other hand, there were seventeen patients died from disease-specific causes. The 1-year estimated overall survival were 92.6%, 2-year and 3-year OS were 77.7% and 74.9%, respectively.

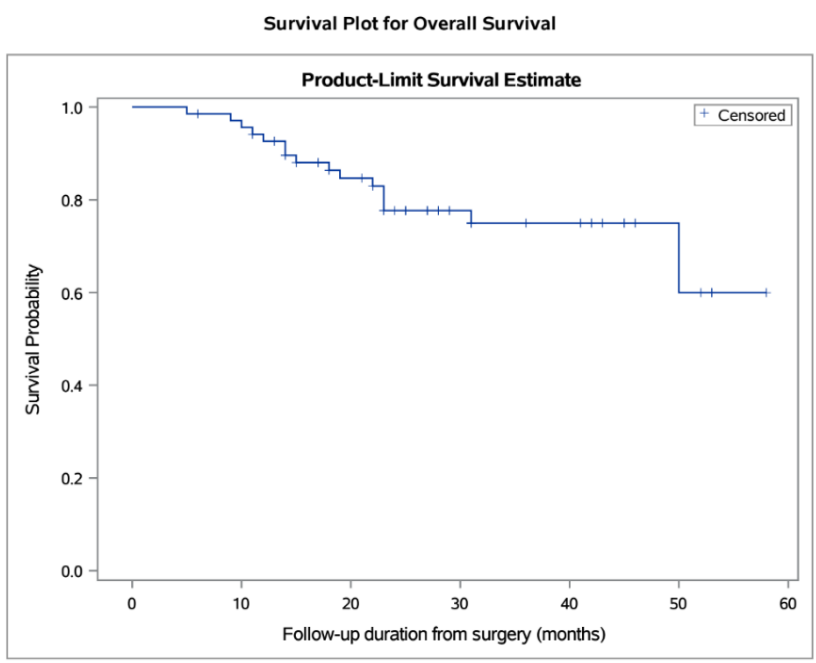

Chart 1. Kaplan–Meier GC survival curve for overall survival in study

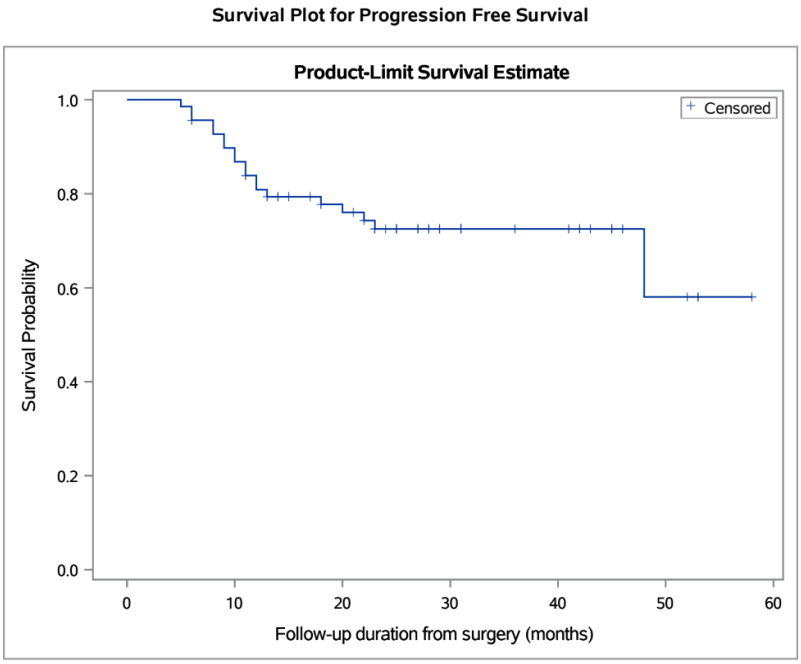

Chart 2. Kaplan–Meier GC survival curve for disease free survival in study

Table 2 shows the results of univariate analyses for correlations between various clinic-pathological factors and outcomes.

At present, univariate analysis using Cox proportional hazards regression analysis showed that in our study there were not significant differences between the clinic-pathology features and outcomes, ($p > 0.05$). Among the clinical factors, the presence of lymphovascular invasion (equal and more than 16) suggested unique significant predictive factors for survival in univariate analysis ($p = 0.0167$) but large Hazard Ratio (11.320) and 95% Confidence Limits (1.552 - 82.561). Hence, we did not perform multivariate analyses to detect significant prognostic predictors.

Table 2. Univariate analyses of clinic-pathological factors for survival in GC patients with adjuvant SOX

Factors	Univariate analysis		
	p value	Hazard Ratio	95% CI
Age	0.9365	1.002	0.948 - 1.060
Gender (female)	0.3067	1.673	0.624 - 4.485
Performance status	0.0559	2.691	0.975 - 7.425
Stage			
IIa	0.9942	11381325	0.000
IIb	1.0000	1.017	0.000
IIIa	0.9942	10737094	0.000
IIIb	0.9939	27830297	0.000
IIIc	0.9939	27085465	0.000

Factors	Univariate analysis		
	p value	Hazard Ratio	95% CI
Differentiation			
Low	0.3422	2.876	0.325 - 25.441
Moderate	0.9941	0.000	0.000
High	0.9950	0.000	0.000
Tumour location			
Antrum	0.9282	1.098	0.143 - 8.451
Pyloric	0.2900	3.042	0.388 - 23.874
Cardia	0.1092	5.725	0.677 - 48.423
Unknown	0.9947	0.000	0.000
Tumour invasion			
T2	0.9936	501,395.4	0.000
T3	0.9928	2,224,329	0.000
T4	0.9934	677,128.2	0.000
Node involvement			
1-2	0.7662	1.347	0.189 - 9.589
3-6	0.3388	2.227	0.432 - 11.488
7-15	0.0562	5.075	0.958 - 26.882
≥ 16	0.0167	11.320	1.552 - 82.561
Number of chemotherapy cycles (< 8)	0.2874	1.737	0.628 - 4.802

IV. DISCUSSION

To the best of our knowledge, this is the first study to evaluate the correlation between clinic-pathological features and outcomes of SOX treatment as adjuvant chemotherapy for Vietnamese patients with gastric cancer. In the present study, we identified clinical and histo-pathological features associated with survival of patients with GC after D2 resection followed by SOX therapy. This patient group showed male dominance, older age, advanced stage cancer at diagnosis, and an undifferentiated histologic tumour type. The chemotherapy completion rate and the median relative dose intensities which suggested the patients' treatment tolerability also were remarkable. In GC patients with adjuvant SOX therapy, lympho-vascular invasion showed a potent of association with poorer outcomes.

Generally, GC is more common in males than females, with a ratio in major surveys ranging from 1.1:1 to 2.3:1.[2,8] Several studies have shown a predominance of female patients in younger patient groups and a predominance of male patients in older patient groups.[9,10] In our present study, patients were predominantly male (60.8%). This difference in the sex ratio

can reflect a protective influence of estrogen against the induction of GC. According to the previous reports by La Vecchia[11] and Palli, risk for GC may increase after a short lifetime of estrogen influence, as was documented for early menopause and a short fertile period.[12] Another possible mechanism for estrogen-mediated prevention of GC incidences is the reduction of gastric acid production. In an experiment on gastric acid secretion with regard to sex hormones, ovariectomy significantly increased parietal cell mass as well as basal acid secretion. Conversely, castration of male rats decreased both the number of parietal cells in the gastric mucosa and basal acid secretion.[13] These findings suggest that estrogen may play a role in the pathogenesis of GC. Other assumptions pertaining to male predominance in GC patients include exposure to carcinogenic factors such as alcohol and/or tobacco assumption, which was more frequent and of longer duration in males than females.[14] Despite of this unique gender ratio, there are no known gender-related differences in GC patient prognosis.[10,15] The present study showed that there were no gender difference and disease prognosis in this GC population. Further studies are needed to elucidate the mechanism of male predominance in GC patients and to determine whether gender influences disease prognosis.

Regarding to GC histologic classifications, undifferentiated type GCs pre-dominated, with values of 68.12%. Histologically, the most common forms of advanced gastric carcinoma are undifferentiated, mostly with signet ring cell and mucinous architecture.[16] Furthermore, the advanced gastric carcinoma which invades into muscularispropria or beyond carries a much worse prognosis, with a 5 year survival rate at about 60% or less.[17] Nonetheless, these data were insufficient for the evaluation of potential associations between GC histologic type and patient survival. These findings suggest that although GC patients typically have an aggressive tumour biology, if they are diagnosed at a favourable disease stage and then proceeded to surgical resection followed by adjuvant therapy, the prognosis would be satisfactory.

Our present results also show that most patients (41 patients, 59.4%) initially presented with advanced stage (stage III) compared to those in stage II (28 patients, 40.6%). The depth of tumour invasion and lympha-vascular involvement were also higher but only greater 16 lymph nodes factor was associated with survival. These differences also may be because of the relatively small sample size and shorter follow-up time. However, this finding is similar to other reports on GC patients and it may be attributable to a lack of screening endoscopy in the typically asymptomatic population.[18,19] Population screening for GC varies between countries in both methods and screening intervals. In Japan, screening for GC is recommended for individuals older than 40 years and involves only a simple risk interview and barium studies. An upper endoscopy is performed if any abnormality is detected. In contrast, in Korea, GC screening every 2 years via either upper gastrointestinal series or upper endoscopy has been recommended for individuals aged 40 years and older. However, these screening criteria do not address populations in Viet Nam; thus, this subgroup of GC patients may be overlooked, leading to a potential delay in diagnosis and worse disease outcomes. Bołdys et al. suggested that in areas of relatively high prevalence of GC, dyspeptic patients younger than 45 years and without alarm.[20] Patients with symptoms should undergo upper gastrointestinal endoscopy in order to avoid any potential delay in GC diagnosis. However, beyond evaluation of symptomatic patients, there should be increased and focused investigations designed to determine an optimal

age threshold for screening endoscopy in the asymptomatic normal population. For early detection, symptomatic young patients should undergo upper gastrointestinal endoscopy, which could help prevent a delay in diagnosis and moreover facilitate adequate intervention and treatment of early-stage disease.

It is thought that the treatment completion rate (76.81%) and the 3-year DFS and OS were 72.5% and 74.9%, respectively in our study was higher than expected and similar to other studies. Kohei Shitara et al. recently reported a phase II trial conducted in Japan to evaluate the tolerability and safety of SOX therapy as adjuvant chemotherapy for Japanese patients with stage III gastric cancer.[21] The treatment completion rate in their study was 74.2% (95%CI: 61.5 - 84.5%) with the standard dose of oxaliplatin they used is 100 mg/m^2 every 3 weeks lower than our study (130 mg/m^2) while the dose of S1 was unchangeable. Guoxiu Wang et al. report on the toxicity and safety analysis of oxaliplatin plus S1 (SOX) treatment for Chinese patients with stage II/III gastric cancer who had received curative D2 gastrectomy.[22] In Wang's study, the six cycles chemotherapy completion rate with the same dose of oxaliplatin and S1 in our study was 72.2% (95%CI: 60.25 - 84.15%) and the 3-year DFS were 75.9%.

Our study also showed that 53 of 69 patients (76.8%) and 14 of 69 patients (20.3%) required dose reduction of oxaliplatin and S1, respectively. Although about two third of the patients required dose reduction of oxaliplatin, the median relative dose intensities were 98.68% for S1 and 93.02% for oxaliplatin in this study. Additionally, 57 of 69 patients (82.6%) required chemotherapy administration to be delayed mainly because of adverse events including gastrointestinal toxicity, thrombocytopenia and peripheral sensory neuropathy. Thus, adverse events caused by adjuvant SOX therapy after curative resection of gastric cancer could be manageable throughout the entire study by dose modification and delay treatment according to the dose reduction criteria that have already been used for advanced gastric cancer. Although there was dose reduction, treatment delay and treatment discontinuation, there was no significant difference in the treatment completion rate and relative dose intensities with patients' survival in univariate analysis. However, this relationship must be cautiously considerate due to the limited patient size and the insufficient surveillance data.

The present study has several limitations. First, this was a single-centre, retrospective study with a relatively small patient size. Further in this study, we did not investigate the efficacy and adverse event, and we do not know whether adjuvant SOX therapy could improve the prognosis of gastric cancer patients compared with XELOX, which is the current standard adjuvant treatment in Vietnam. A randomized controlled trial is required to evaluate the efficacy of adjuvant SOX therapy.

V. CONCLUSION

In conclusion, GC patients in Vietnam have clinic-pathological features such as male dominance, advanced stage cancer, and undifferentiated histologic type. Although adjuvant SOX therapy is effective and manageable with optimal dose reduction and delay in selected patients with curative resection of gastric cancer, further investigations are warranted to evaluate the efficacy and the safety of SOX as adjuvant chemotherapy in larger studies.

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