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Elevated serum plasma fibrinogen is associated with advanced tumor stage and poor survival in hepatocellular carcinoma patients

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Abstract

Hyperfibrinogenemia has been reported to be a predictor of poor prognosis in cancer patients, and in hepatocellular carcinoma (HCC) patients, survival remains uncertain and unpredictable. The aim of the present study was to evaluate the association between the level of plasma fibrinogen and overall survival in HCC patients.

Overall, 308 patients with histologically proven HCC were included in our study. Univariate and multivariate analyses were performed to identify predictive risk factors for the rates of overall survival and tumor recurrence.

Patients in the high-fibrinogen-level group were more likely to have advanced stage HCC, portal vein invasion, and tumors that were greater in number and larger in diameter than were patients in the low-fibrinogen-level group (all $P < .05$). The long-term overall survival rate of patients in the high-fibrinogen group was much lower than that of patients in the normal-fibrinogen group ($P = .008$), and similar outcomes were observed in the subgroup of patients who underwent radical therapies for HCC ($P = .003$). The results of the univariate and multivariate analyses indicated that high plasma fibrinogen remained independently associated with poorer overall survival. In addition, high plasma fibrinogen levels were associated with nonresponse to transarterial chemoembolization (TACE) ($P < .001$).

Elevated plasma fibrinogen was independently associated with advanced HCC stage, poor prognosis, and nonresponse to TACE and may, therefore, serve as a valuable clinical biomarker for predicting prognosis in HCC patients.

Abbreviations: AFP = alpha fetal protein, BCLC = Barcelona clinic liver cancer classification, CR = complete response, ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, mRECIST = amended response evaluation criteria in solid tumors, PD = progressive disease, PR = partial response, RFA = radiofrequency ablation, SD = stable disease, TACE = transarterial chemoembolization.

Keywords: hepatocellular carcinoma, plasma fibrinogen, survival

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide[1] and the fourth leading cause of cancer death in China.[2] Radical therapies, including surgical resection, liver transplantation, and radiofrequency ablation, are the standard modality used for the curative treatment of HCC; however, the application of these therapies is limited due to the impaired liver function and advanced tumor stage of patients and a shortage of donors.[3] According to the Barcelona Clinic Liver Cancer classification (BCLC) system, transarterial chemoembolization (TACE) and sorafenib are the recommended adjuvant therapies for intermediate and advanced HCC. The duration of overall survival predicted in these patients is often less than 5 years; therefore, it would be useful to identify novel biomarkers that may facilitate the prediction of outcomes and selection of patients who would most likely benefit from treatment.

An increasing number of studies have focused on the association between hypercoagulation and malignancy progression. Recent studies have provided strong evidence that plasma fibrinogen is associated with tumor progression and poor prognosis in lung cancer,[4] breast cancer,[5] gastric cancer,[6] ovarian cancer,[7] oral and oropharyngeal cancer,[8] biliary tract cancer,[9] and penile cancer[10] patients. Fibrinogen is a 340-kDa glycoprotein that is synthesized in the liver and converted into fibrin by active thrombin.[11] A limited number of studies have investigated the level of fibrinogen as a prognostic biomarker for overall survival and tumor recurrence in HCC patients[12–14]; however, all of the participants included in these studies have been early stage HCC patients who had undergone liver transplantation or liver resection. To our knowledge, the present study is the first to evaluate the significance of plasma fibrinogen as a predictor of overall survival and tumor recurrence in HCC

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patients. The purpose of this study was to assess the association between the level of plasma fibrinogen and tumor stage and evaluate the value of plasma fibrinogen in predicting overall survival and adjuvant therapy response in HCC patients.

2. Patients and methods

Our retrospective study included 1086 HCC patients who were diagnosed and treated in our hospital. Eligibility for inclusion in the present study was defined by the following criteria: age equal to or greater than 18 years and diagnosed with HCC in our hospital. The following exclusion criteria were applied: loss to follow-up; lack of plasma fibrinogen data at diagnosis; insufficient extractable data; and diagnosis of hepatic cholangiocarcinoma, metastastic liver cancer, or hematological disease. Based on these inclusion and exclusion criteria, data from 308 cases of HCC were included and analyzed in the present study. The study was approved by our departmental review board and conducted in accordance with the 1990 Declaration of Helsinki and its subsequent amendments, and all patients or their families provided signed informed consent. An enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was used to diagnose HCC in routine practice; additionally, arterial hypervascularization in all or part of the tumor, washout in the portal-venous phase, and elevated serum fetoprotein levels (>200 ng/mL) were used to facilitate the diagnosis of HCC.

After diagnosis, all patients were followed up until death or the cutoff date (Oct 30, 2016) by outpatient clinic consultation, inpatient therapy, or communication via telephone, e-mail, or WeChat. The primary outcomes were overall survival, which was calculated as the duration from the date of diagnosis in our hospital to the date of death, and tumor-free survival, which was calculated as the duration from the date of resection to the date of tumor recurrence. The secondary outcome in the present study was response to adjuvant therapies, including TACE and sorafenib, which was examined overall as well compared between subgroups that were categorized according to BCLC stage (A, B, or C). Baseline and tumor characteristics, treatment, and follow-up data for the patients were extracted and analyzed.

The assessment of fibrinogen levels was included within the routine blood examinations performed on all HCC patients who were first diagnosed in our hospital as most cases of HCCs were caused by hepatitis B virus and observed in conjunction with liver cirrhosis. Blood samples were obtained via cubital vein puncture after 8 hours of fasting and then sent to the clinical laboratory of our hospital and analyzed using the Clauss method and Dimension Vista System (Siemens Healthcare Diagnostics, Eschborn, Germany) according to the manufacturer's instructions. In our hospital, normal plasma fibrinogen levels were defined as those between 2.0 and 4.0 g/L, and hyperfibrinogenemia was defined as plasma fibrinogen concentrations greater than 4.0 g/L. Patient response to TACE was evaluated based on the amended response evaluation criteria in solid tumors (mRECIST) definitions and graded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).[15]

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as percentages (%). Univariate and multivariate Cox regression models were generated for the primary and secondary outcomes. The Kaplan–Meier method and Cox proportional hazard analysis were used for the analysis of overall and tumor-free survival rates. All data analyses was performed using the SPSS 17.0 software package (SPSS, Chicago, IL), and $P < .05$ was considered statistically significant.

3. Results

3.1. Patient and tumor characteristics

The baseline characteristics of study patients both overall and grouped according to fibrinogen level (normal or high) are listed

Table 1

Comparison of baseline and tumor characteristics between the normal and high plasma fibrinogen level groups.

Variables	All patients N = 308	Normal fibrinogen N = 212	High fibrinogen N = 96	P
Age at diagnosis (y)	51.2 ± 12.9	50.5 ± 13.0	52.7 ± 12.6	.161
Gender (M/F)	220/88	147/65	78/18	.110
BMI (kg/M^2)	23.6 ± 2.3	23.5 ± 2.3	23.8 ± 2.3	.263
Underlying liver disease (None/HBV/HCV/alcohol)	10/281/10/12	3/195/5/9	2/86/5/3	.523
Child-Pugh score (A/B/C)	204/57/47	141/41/30	63/16/17	.743
MELD score	8.9 ± 4.8	8.8 ± 4.6	9.3 ± 5.1	.379
ECOG score (0/1/2/3/4)	174/39/49/33/13	124/31/30/20/7	50/8/19/13/6	.106
Portal hypertension (yes/no)	268/40	173/39	85/11	.592
AFP level (ng/mL)	1119.6 ± 4902.5	1163.8 ± 5516.4	1022.1 ± 3172.8	.815
Tumor number	2.4 ± 1.4	2.2 ± 1.5	2.6 ± 1.4	.015*
Single/multiple	117/191	92/120	30/56	.022*
Total tumor diameter (cm)	9.6 ± 3.9	8.8 ± 3.3	11.5 ± 4.5	<.001**
Portal vein invasion (yes/no)	76/232	54 (25.5%)	38 (39.6%)	.043*
I	35	23	12	
II	18	8	10	
III	20	14	6	
IV	19	9	10	
HCC stage (A/B/C/D)	61/124/69/54	47/86/44/35	14/38/25/19	.038*
Therapy (RFA/Resection/TACE/Sorafenib/others)	16/46/217/10/19	12/30/150/6/14	4/16/67/4/5	.896
Plasma fibrinogen level	3.4 ± 0.9	2.9 ± 0.5	4.5 ± 0.3	<.001**

AFP = alpha fetal protein, BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

* $P < 0.05$.

** $P < 0.05$.

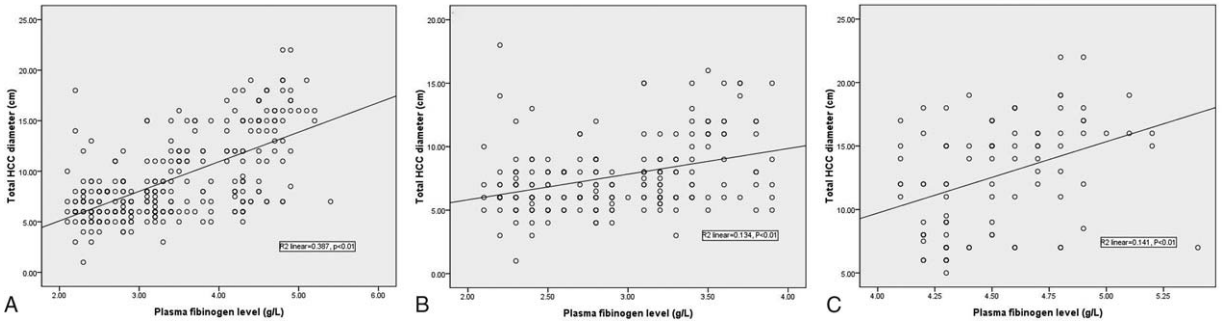

Figure 1. Correlation between HCC diameter and plasma fibrinogen level. A: The scatter plot shows that total HCC diameter was linearly correlated with plasma fibrinogen level in the 308 patients (linear $R^2 = 0.387$, $P < .01$); B: the scatter plot shows that total HCC diameter was linearly correlated with plasma fibrinogen level in the normal-fibrinogen group (linear $R^2 = 0.134$, $P < .01$); C: the scatter plot shows that total HCC diameter was linearly correlated with plasma fibrinogen level in the high-fibrinogen group (linear $R^2 = 0.141$, $P < .01$). HCC = hepatocellular carcinoma.

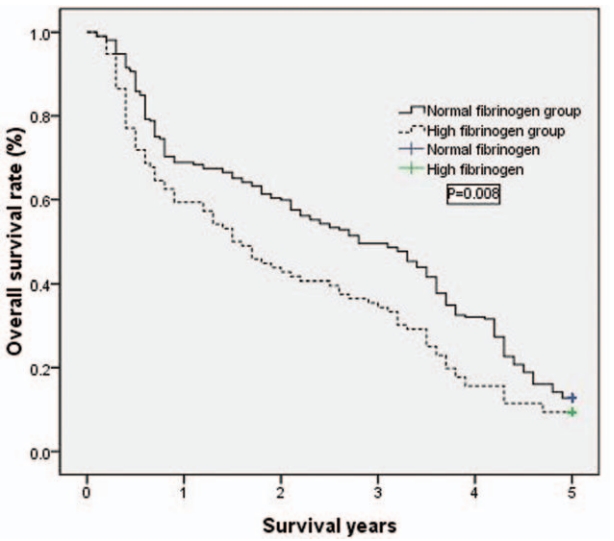

Figure 2. Comparison of overall survival: HCC patients with high serum-fibrinogen levels demonstrated significantly poorer long-term overall than did patients with normal fibrinogen levels ($P < .01$). HCC = hepatocellular carcinoma.

in Table 1. Patients in the high-fibrinogen group were more likely to have advanced stage HCC ($P = .038$), portal vein invasion ($P = .043$), tumors that were greater in number ($P = .015$) and tumors that were larger in diameter ($P < .001$) than were patients in the low-fibrinogen group. No other baseline or tumor characteristics differed significantly between patients with normal and high fibrinogen levels (all $P > .05$). Additionally, total HCC diameter was linearly correlated with the plasma fibrinogen level in all 308 patients (as shown in Fig. 1A, linear $R^2 = 0.387$, $P < .01$) and in the subgroups: normal-fibrinogen group (as shown in Fig. 1B, linear $R^2 = 0.134$, $P < .01$) and high-fibrinogen group (as shown in Fig. 1C, linear $R^2 = 0.141$, $P < .01$).

3.2. Overall survival rate and tumor-free survival rate

As shown in Fig. 2, the rate of long-term overall survival in patients in the normal-fibrinogen group was much higher than that of patients in the high-fibrinogen group ($P = .008$), with 1-, 3-, and 5-year overall survival rates of 67.3%, 47.0%, and 12.7%, respectively, identified in the normal-fibrinogen group and 59.4%, 34.4%, and 9.4%, respectively, identified in the high-fibrinogen group. In the subgroup of patients who underwent liver resection or RFA for HCC, patients in the high-fibrinogen group also had significantly lower rates of overall survival (as shown in Fig. 3A, $P = .003$) and tumor-free survival (as shown in Fig. 3B, $P = .002$) than did patients in the normal-fibrinogen group.

3.3. Univariate and multivariate analyses of predictive factors for overall survival

The results of the univariate and multivariate Cox proportional hazards regression analyses of prognostic factors for overall

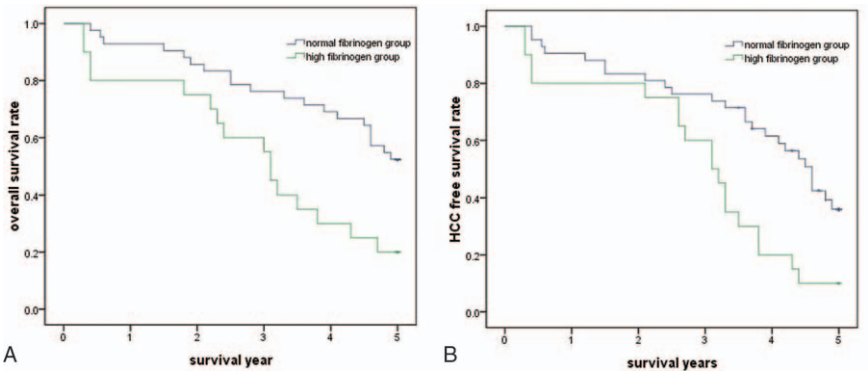

Figure 3. Comparison of overall and tumor-free survival: HCC patients with high serum fibrinogen levels who underwent radical therapies demonstrated significantly poorer long-term overall (A) and tumor-free (B) survival than did patients with normal fibrinogen levels (all $P < .01$). HCC = hepatocellular carcinoma.

Table 2

Univariate and multivariate analyses of predictive factors for long-term survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis (<40 vs. ≥40 years)	1.33	0.89–1.76	.321			
Gender (M vs. F)	1.28	0.91–1.55	.467			
BMI (<24 vs. ≥24 kg/M^2)	1.55	0.78–2.28	.832			
Underlying liver disease (HBV vs. other)	1.12	0.89–1.32	.476			
Child score (A/B vs. C)	1.89	0.87–3.11	.765			
MELD score (<10 vs. ≥10)	0.82	0.68–0.96	.048*	0.97	0.58–1.22	.286
ECOG score (0–1 vs. 2–4)	1.98	0.89–2.88	.367			
Portal hypertension (yes vs. no)	1.87	0.92–2.77	.271			
AFP level (<400 vs. ≥400 ng/ml)	1.26	0.92–2.21	.563			
Tumor number (single vs. multiple)	0.82	0.67–0.96	.046*	0.86	0.67–1.28	.117
Total tumor diameter (<10 vs. ≥10 cm)	0.82	0.68–0.92	.086			
Portal vein invasion (yes vs. no)	3.22	0.95–6.77	.098			
HCC stage (A vs. B–D)	0.68	0.55–0.86	.036*	0.82	0.68–0.96	.042*
Therapy (RFA or resection vs. others)	0.72	0.63–0.88	.006*	0.81	0.72–0.90	.028*
Plasma fibrinogen level (≤4 vs. >4 g/L)	0.52	0.38–0.76	<.001**	0.62	0.41–0.83	.001**

AFP = alpha fetal protein, BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, MELD = model for end-stage liver disease, RFA = radiofrequency ablation.

* $P < 0.05$.

** $P < 0.05$.

survival are shown in Table 2. In the univariate analysis, significantly poorer overall survival was identified in patients who had a model of end-stage liver disease (MELD) score equal to or greater than 10, had intermediate or advanced stage HCC (BCLC B-D), underwent adjuvant therapies (therapies other than RFA or resection), and had a plasma fibrinogen level >4 g/L when compared with their respective counterparts. In multivariate analysis, high levels of plasma fibrinogen remained independently associated with poorer overall survival.

3.4. Response to TACE

TACE was the most commonly used adjuvant therapy for intermediate or advanced HCC, and 217 HCC patients underwent at least 1 course of TACE, as shown in Table 3. After the first course of TACE, the rate of partial or complete response to TACE was significantly greater in the normal-fibrinogen group (62.7%) than that in the high-fibrinogen group (38.8%, $P = .001$). Similar differences were observed at 5 years post-TACE ($P < .001$).

Table 3

A comparison of responses to TACE between patients with normal fibrinogen and high fibrinogen.

Responses	Normal fibrinogen N = 150	High fibrinogen N = 67	*P*
First course of TACE			.001**
Complete response (CR)	45 (30.0%)	10 (14.9%)	
Partial response (PR)	49 (32.7%)	16 (23.9%)	
Stable disease (SD)	21 (14.0%)	13 (19.4%)	
Progressive disease (PD)	35 (23.3%)	28 (41.8%)	
Overall 5-year response to TACE			<.001**
Complete response (CR)	53 (35.3%)	12 (17.9%)	
Partial response (PR)	57 (38.0%)	16 (23.9%)	
Stable disease (SD)	15 (10.0%)	17 (25.3%)	
Progressive disease (PD)	25 (16.7%)	22 (32.8%)	

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease, SD = standard deviation, TACE = transarterial chemoembolization.

** $P < 0.05$.

4. Discussion

In the present study, we evaluated the prognostic value of plasma fibrinogen in a large cohort of HCC patients. We found high plasma fibrinogen levels to be associated with tumors that were greater in number and larger in size; more advanced HCC, which is consistent with previous reports regarding other human cancers[7,16–18]; and an increased frequency of portal vein invasion, which may indicate that increased plasma fibrinogen levels are associated with increased tumor growth and progression. Second, our results demonstrated that patients with high plasma fibrinogen levels had lower rates of overall survival and tumor-free survival, and most importantly, patients with elevated plasma fibrinogen levels demonstrated poorer response to TACE. Our findings indicate that plasma fibrinogen may be a significant prognostic marker in HCC. A number of parameters have been identified as prognostic factors in HCC, such as AFP[19]; however, previously identified factors are not components of routine practice and are prohibitively expensive to perform in most hospitals, whereas plasma fibrinogen is an established laboratory parameter that is commonly used in routine practice and relatively inexpensive.

Tumor progression occurs as a consequence of complex interactions between tumor cells, the environment, and inflammatory responses.[20] There are several theories that may explain our findings. First, fibrinogen is an important component in the final step of the coagulation pathway.[21] High levels of serum fibrinogen may be associated with increased fibrinogen deposits in tumor tissue and serve as an extracellular matrix for tumor cell adhesion or migration, which may lead to tumor metastasis,[22] promote tumor neovascularization and angiogenesis, enhance adhesion and invasion,[23] and play an important role in cancer progression. As shown in our results, HCC patients with high levels of serum fibrinogen were more likely to have tumors that were greater in number and larger in diameter than were those with normal levels, and, most importantly, they were more likely to have portal vein invasion. Our results are in accordance with previous studies of other types of tumors.[9,24] The mechanism underlying this association may be the binding of fibrinogen to

members of the transforming growth factor-B, vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor gene families, thereby leading to the inhibition of apoptosis, angiogenesis, and metastasis and promotion of tumor cell proliferation.[8,25] Platelet-fibrin microthrombi appear to act as a physical barrier, preventing contact between natural killer cells and tumor cells.[26] Moreover, fibrinogen acts as a bridging factor between tumor and host cells and enhances the endothelial adhesion of tumor cell emboli in the vasculature of target organs.[27] A previous study suggested that tumor cells may have the ability to produce endogenous fibrinogen,[28] which may explain the finding that serum fibrinogen levels were linearly correlated with tumor diameter and tumor number. Furthermore, anticoagulants such as warfarin and heparin have been found to exhibit antitumor and antimetastatic properties both in vivo and in vitro.[29]

Second, fibrinogen is an acute phase protein that is released in response to infection or systemic inflammation, and it is known that tumors are closely associated with chronic inflammatory responses.[30] Fibrinogen may induce the synthesis of interleukin-6, an inflammatory mediator, or interact with leukocytes.[31] Therefore, hyperfibrinogenemia may occur secondary to chronic inflammation that occurs in response to tumor progression. Fibrinogen may also mediate the adhesion of leukocytes to endothelial cells and the production of pro-inflammatory cytokines in peripheral blood mononuclear cells,[32] and fibrinogen-leukocyte integrin receptor a Mb2 interactions may induce a fibrinogen-dependent inflammatory response, thereby leading to the pathogenesis and progression of tumors.[33] Other systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have been reported to serve as prognostic factors for different human cancers.[32,34]

Our results indicated that elevated plasma fibrinogen levels were associated with poorer long-term overall survival and tumor-free survival. These findings are in accordance with previous reports regarding other malignancies, such as lung,[35] esophageal,[36] gastric,[37] colorectal,[34] and ovarian[7] cancer. Most importantly, high plasma fibrinogen levels have been correlated with poor response to therapy, including response to trastuzumab treatment in HER2-positive breast cancer.[38] In the present study, we assessed the value of plasma fibrinogen levels in the prediction of response to TACE in HCC patients. To our knowledge, this is the first study to evaluate this aspect of plasma fibrinogen. Our findings, which are consistent with the results of previous studies,[7,36] indicated that high serum fibrinogen levels were associated with advanced stage HCC, tumor progression, and poorer long-term outcomes, including recurrence and survival. Therefore, serum fibrinogen may serve as a useful biomarker for the identification of advanced HCC, a predictor of long-term overall survival and tumor recurrence, and most importantly, a criterion for the selection of candidates for therapies such as TACE.

Our study has several limitations. First, the retrospective nature of the present study cannot be ignored, even with the application of strict inclusion and exclusion criteria to minimize the risk of potential biases. Second, the limited number of HCC patients included and the analysis of data from a single center may also weaken the conclusions of our study. Third, the correlation between the level of fibrinogen in the tumors and in plasma was not presented in our present study, however, this may be our following work. A multicenter cohort study with a large sample of patients is being performed in 7 centers in mainland China, and more objective results and conclusions will likely be derived from this prospective study.

In conclusion, the results of our single-center study indicated that high plasma fibrinogen levels were associated with advanced stage HCC and poorer long-term overall survival, tumor-free survival, and response to adjuvant therapies such as TACE. Prospective and multicenter cohort studies that include large samples of patients should be conducted to confirm the prognostic significance of serum plasma fibrinogen levels in HCC patients.

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