IS HIGH-DENSITY LIPOPROTEIN A PREVENTIVE FACTOR FOR VENOUS THROMBOEMBOLISM IN PATIENTS WITH LUNG CANCER

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ABSTRACT

Introduction*: Lung cancer is a malignant tumor with the highest mortality and morbidity, and its common complication is venous thromboembolism (VTE). We aim to investigate the blood lipid level, demographic data, and related risk factors of patients with lung cancer-related VTE, and provide meaningful biomarkers for its early prevention.*

Materials and methods*: All study subjects were from newly diagnosed lung cancers with VTE who were hospitalized in the Guangxi Medical University Cancer Hospital between December 2013 and December 2019. Using propensity score matching (PSM) (1 to 1 ratio), a total of 89 VTE groups and 89 non-VTE groups were included in the data analysis. Univariate analysis of blood lipids, baseline data, and related hematological indicators of the two groups, and the independent risk factors were screened out through binary classification logistics regression.*

Results*: In multivariate logistics regression, independent risk factors for VTE in lung cancer included stage IV patients, elevated leukocyte (>9.5x10*9/L), and high levels of D dimer(>1.44mg/L). Increased levels of leukocyte and D dimer had moderate predictive value for VTE [AUC 0.802 (95% CI, 0.739-0.866)]. For patients younger than 65, high-density lipoprotein (HDL) ≥ 1 mmol/L were associated with a lower risk of VTE, and high levels of HDL (≥1 mmol/L) had a lower risk of VTE than low levels of HDL (<1 mmol/L) (OR 0.138, 0.035-0.544).*

Conclusion*: In patients with lung cancer, elevated leukocyte and D dimer may increase the risk of VTE. High levels of HDL may decrease the risk of VTE, and HDL is a possible protective factor.*

Keywords: *lung cancer, venous thromboembolism, blood lipids, high-density lipoprotein, propensity score matching.*

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Introduction

Tumor-associated venous thromboembolic disease (TAVTE) is defined as a malignant tumor with the venous thromboembolic disease (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT). The occurrence of VTE often indicates a poor prognosis and decreased quality of life. The incidence of VTE is increasing year by year[1]. The risk of VTE for malignant tumors is four to seven times that of non-tumor patients[2]. The incidence of VTE in different types of tumors ranges from 4-20%. Among them, the incidence of pancreatic cancer, lung cancer, gastrointestinal tumors, and ovarian cancer is higher. If considering asymptomatic or undetected thrombosis, the incidence is even higher[3]. Patients who are diagnosed with active tumors for the first time have a higher risk of VTE occurrence than in other periods. Most patients have VTE events within the first three months and reach the peak of the cumulative incidence in six months[4]. VTE has become the

second leading cause of death in cancer patients, and the first is cancer progression[5]. Patients with TAVTE have a three-fold increased risk of death rate compared to non-tumor patients with VTE[6].

Lung cancer is a malignant tumor with the highest morbidity and mortality in the world[7], therefore it is imperative to investigate lung cancer-related VTE. In recent years, more and more risk factors for lung cancer-related VTE have been reported[8-12], such as age, race, tumor type, disease stage, and other factors, treatment factors such as chemotherapy and surgery, as well as systemic diseases such as diabetes and hypertension. The exploration of potential risk factors can help reduce the risk of VTE in lung cancer patients.

Dyslipidemia is an important factor affecting the formation of arterial thrombosis, and previous studies have confirmed that HDL is negatively related to the risk of cardiovascular events[13]. Dyslipidemia is also associated with VTE, as a study reported that elevated HDL was negatively correlated with PE in non-tumor patients[14], and high levels of HDL might reduce the risk of recurrent VTE[15]. However, some studies had failed to confirm the risk relationship between HDL and VTE[16,17]. For tumor patients, especially lung cancer patients, the relationship between blood lipids and VTE is still being explored. Through the analysis of blood lipid levels in patients with lung cancer and VTE, we can understand whether dyslipidemia is a risk factor for lung cancer-related VTE.

Material and methods

The study was conducted by the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of the Affiliated Tumor Hospital of Guangxi Medical University. Because of the retrospective nature of the study, patient consents for inclusion were waived.

Patients

Lung cancer is diagnosed by histology or cytology pathology, and TNM staging adopts the AJCC 8th edition lung cancer staging. Patients diagnosed with primary lung cancer were selected at the Affiliated Tumor Hospital of Guangxi Medical University. VTE diagnostic criteria were the following: pulmonary embolism (PE) diagnosed by pulmonary CT angiography (CTPA), deep vein thrombosis (DVT) diagnosed by venous compression ultrasound (CUS).

Those with VTE from December 2013 to December 2019 were in the case group, and those without VTE were in the control group. The case group included incidentally diagnosed and symptomatic as an inpatient, and case samples diagnosed with VTE before anti-tumor treatment. We used the following inclusion criteria: patients who were pathologically diagnosed with lung cancer, and did not use anticoagulation, antiplatelet drugs, or lipid-lowering agents, and no central venous catheter or infusion port implantation; no anti-tumor therapy before or after hospitalized (including radiotherapy and chemotherapy, surgery, targeted, immunotherapy and hormone therapy, etc). And the exclusion criteria were: hypertension, diabetes, hyperlipidemia, coronary heart disease, liver disease, cerebrovascular disease, and active infection, or a history of thrombosis (more than three months before the diagnosis of lung cancer); double cancer or compound cancer, or lacking data (Figure 1).

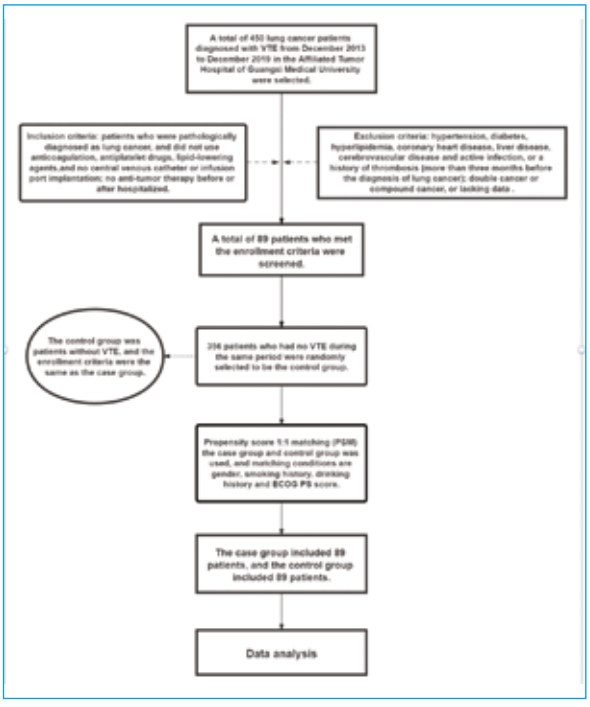

Figure 1: Flowchart of study design.

Study design

The electronic medical record system of Guangxi Medical University Affiliated Tumor Hospital was used to collect the data. Collect baseline data were: gender, age, smoking history, drinking history, tumor pathology type, tumor stage(TNM), Eastern Cooperative Oncology Group Performance Status Score(ECOG PS), body mass index(BMI). Blood indicators were: leukocyte or white blood cells(WBC), red blood

cells(RBC), hemoglobin(HGB), platelets(PLT), neutrophil ratio(NEU%), albumin(ALB), total cholesterol(CHO), triglycerides(TG), HDL, low-density lipoprotein (LDL), apolipoprotein A1(APO-A), apolipoprotein B(APO-B), apolipoprotein A1 vs apolipoprotein B(A1/B), lipoprotein a(LPa), lactate dehydrogenase(LDH), total bile acid(TBA), urea, creatinine(CREA), endogenous creatinine clearance(GFR), D dimer(DD), Creatine kinase(CK), creatine kinase isoenzyme(CK-MB), homocysteine(HCY).

Statistical analysis

All statistical analysis was performed with IBM SPSS 20 program. Propensity score 1:1 matching (PSM) the case group and control group was used, and matching conditions are gender, smoking history, drinking history, and ECOG PS score. The measurement data obeyed a normal distribution and were described by the mean ± standard deviation, and the qualitative data were described by the percentage, and the difference between the two groups was described by the X2 test or T test. Logistic regression was used to perform univariate analysis of relevant laboratory indicators, factors with p>0.05 were included in the multivariate logistic regression analysis, independent risk factors for VTE were screened, and the forest plot was drawn using GraphPad Prism 5. The receiver operating curve (ROC) for the independent risk factors was screened by the logistics regression, and the cut-offs with sensitivities and specificities were identified by ROC.

Results

A total of 450 lung cancer patients diagnosed with VTE from December 2013 to December 2019 in the Affiliated Tumor Hospital of Guangxi Medical University were selected, and a total of 89 patients who met the enrollment criteria were screened. A total of 356 patients who had no VTE during the same period were randomly selected to be the control group, and their baseline data and hematological indicators were recorded. Using propensity score matching (PSM) (1 to 1 ratio), a total of 89 patients were included in the case group (including 24 cases of PE, 60 cases of DVT, 5 cases of PE combined with DVT), and 89 cases of the matched control group. There was no significant difference in gender, smoking history, drinking history and ECOG PS score between the two groups after PSM (Table 1).

		case group (n=89)	control group (n=89)	X^2	P
Sex	Male	58 (51.3)	55 (48.7)	0.218	0.640
	Female	31(47.7)	34 (52.3)		
Smoking history	Yes No	42 (47.7) 47 (52.2)	46 (52.3) 43 (47.8)	0.36	0.549
Drinking history	Yes	17 (53.1)	15 (46.9)	0.152	0.696
	No	72 (49.3)	74 (50.7)		
ECOG PS (score)	0-1 2-3 4-5	71 (50)	71(50)	0	1.000

Table 1: Comparison of baseline data after PSM.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status Score.

Among the baseline indicators, the age and tumor stage of the two groups were significantly different (p<0.001), and the histological type and BMI were not statistically different (p>0.05) (Table 2).

		case group (n=89)	control group (n=89)	X^2	P
Age(years)	≥65	18(19.4)	75(80.6)	73.15	**<0.001**
	<65	71(83.5)	14(16.5)		
BMI	<18.5	11(57.9)	8(42.1)	1.041	0.594
	18.5-24	57(50.9)	55(49.1)		
	≥24	21(44.7)	89(50)		
TNM stage	I-III	20(31.3)	44(68.8)	14.053	<0.001
	IV	69(60.5)	45(39.5)		
Histological type	SCLC	6(37.5)	10(62.5)	1.099	0.295
	NSCLC	83(51.2)	79(48.8)		

Table 2: Baseline indicators need to be observed after PSM.
Abbreviations: BMI, body mass index; NSCLC, Non-Small Cell Lung Cancer; SCLC, Small Cell Lung Cancer.

	case group (n=89)	control group (n=89)	OR(95%CI)	P
WBC (10*9/L)	10.11±5.46	7.29±2.34	1.285(1.14-1.45)	**<0.001**
RBC (10*12/L)	4.40±0.64	4.48±0.59	0.797(0.492-1.291)	0.356
HGB (g/L)	122.24±18.22	127.01±18.44	0.986(0.97-1.002)	0.087
PLT (10*9/L)	283.5±85.66	293.56±82.46	0.999(0.995-1.002)	0.424
NEU (%)	72.08±9.39	64.52±10.44	1.079(1.044-1.116)	**<0.001**
ALB(g/L)	35.60±4.95	38.35±4.44	0.883(0.826-0.945)	**<0.001**
CHO (mmol/L)	4.92±0.84	5.04±0.90	0.851(0.606-1.195)	0.351
TG (mmol/L)	1.53±1.18	1.44±0.83	1.093(0.809-1.476)	0.562
HDL (mmol/L)	1.10±0.23	1.20±0.25	0.185(0.052-0.662)	**<0.01**
LDL (mmol/L)	3.28±0.74	3.23±0.76	1.087(0.735-1.607)	0.677
APO-A(g/L)	1.11±0.28	1.21±0.22	0.209(0.058-0.756)	**<0.05**
APO-B(g/L)	1.07±0.31	1.01±0.23	2.433(0.737-8.032)	0.144
A1/B	1.13±0.54	2.00±1.37	0.312(0.168-0.58)	**<0.001**
LPa (mg/L)	428.52±329.62	287.10±274.30	1.002(1.001-1.003)	**<0.01**
LDH(U/L)	333.33±192.11	228.30±103.97	1.006(1.003-1.009)	**<0.001**
TBA(umol/L)	6.66±10.23	5.15±5.26	1.025(0.984-1.067)	0.232
UREA(mmol/L)	5.21±1.59	5.11±1.64	1.04(0.867-1.248)	0.674
CREA(umol/L)	74.52±19.74	73.44±17.79	1.003(0.987-1.019)	0.700
GFR(ml/min/1.7)	83.65±22.07	85.37±22.26	0.996(0.983-1.01)	0.604
DD (mg/L)	6.23±6.16	1.74±2.83	1.275(1.158-1.404)	**<0.001**
CK(U/L)	81.3±81.74	93.42±69.19	0.998(0.994-1.002)	0.293
CK-MB(U/L)	16.25±13.70	15.66±12.41	1.003(0.981-1.026)	0.765
HCY(umol/L)	16.33±11.46	14.53±7.28	1.021(0.987-1.057)	0.227

Table 3: Related hematological indicators after PSM.
Abbreviations: APO-A, apolipoprotein A1; APO-B, apolipoprotein B; A1/B, apolipoprotein A1 vs apolipoprotein B; ALB, albumin; CHO, total cholesterol; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; CREA, creatinine; DD, D dimer; GFR, endogenous creatinine clearance; HCY, homocysteine; HDL, high density lipoprotein; HGB, hemoglobin; LDL, low density lipoprotein ; Lpa, lipoprotein a; LDH, lactate dehydrogenase; NEU, neutrophil; PLT, platelets ; RBC, red blood cells; TG, triglycerides; TBA, total bile acid ; UREA, urea; WBC, leukocyte.

In the univariate analysis, the two groups of WBC, NEU%, ALB, HDL, A1/ B, LPa, LDH, and D dimer are significantly different (p<0.01). There was statistical significance in APO-A of the two groups (p<0.05). The case group has higher WBC

(10.11 ± 5.46), NEU% (72.08 ± 9.39), and D dimer (6.23 ± 6.16), but HDL (1.1 ± 0.23), APO-A (1.11 ± 0.28), and A1/B (1.13 ± 0.54) in the case group were lower than those in the control group. There was no statistical difference in CHO, TG, HDL and APO-B between the two groups (Table 3)

In the binary logistics regression of multivariate analysis, stage IV, WBC>9.5x10*9/L and D dimer >1.44 mg/L were independent risk factors for VTE in patients with lung cancer. Patients with stage IV, WBC>9.5x10*9/L and D dimer>1.44 mg/L had significantly increased risk of VTE (OR 5.581, 4.772, 4.339, respectively). Patients ≥65 years had a lower risk of VTE than patients <65 years. In terms of blood lipids, HDL ≥1 mmol/L had a lower risk of VTE than HDL<1 mmol/L (OR 0.138, 95%CI 0.035-0.544), and the difference was statistically significant (p<0.01)(Table 4).

		B	SE	Wals	P	OR(95%CI)
Age (years)	≥65 <65	-3.737	0.608	37.726	**<0.001**	**0.024(0.007-0.079)**
TNM stage	IV I-III	1.719	0.576	8.910	**<0.01**	**5.581(1.805-17.256)**
WBC (10*9/L)	>9.5 ≤9.5	1.563	0.651	5.758	**<0.05**	**4.772(1.332-17.100)**
NEU (%)	>75 ≤75	0.654	0.631	1.073	0.300	1.923(0.558-6.628)
ALB (g/L)	≥35 <35	0.655	0.594	1.218	0.270	1.926(0.601-6.168)
LDH (U/L)	>245 ≤245	0.763	0.540	1.996	0.158	2.145(0.744-6.186)
HDL (mmol/L)	≥1 <1	-1.982	0.701	8.000	**<0.01**	**0.138(0.035-0.544)**
APO-A(g/L)	>1.32 ≤1.32	0.195	0.667	0.085	0.770	1.215(0.329-4.492)
A1/ B	≥1 <1	-0.160	0.633	0.064	0.801	0.852(0.247-2.945)
LPa (mg/L)	≥300 <300	0.526	0.522	1.015	0.314	1.692(0.608-4.703)
DD (mg/L)	>1.44 ≤1.44	1.468	0.517	8.043	**<0.01**	**4.339(1.574-11.963)**
constant		0.033	0.993	0.001	0.974	1.033

Table 4: The binary logistics regression of multivariate analysis.

In the forest plot, age and HDL were on the left side of the Y-axis, which represents protective factors, and stage, WBC, and D-dimer were on the right side of the Y- axis, which represent risk factors (Figure 2). HDL is a possible protective factor for VTE.

In Figure 3, we plotted the receiver operating curve (ROC) of the independent risk factors for VTE formation (white blood cell count and D-dimer level) to evaluate their predictive value for lung cancer VTE formation. WBC had predictive values for VTE (AUC=0.697, 95%CI 0.624-0.764), and D dimer had medium predictive values for VTE occurrence (AUC=0.761,95%CI 0.692-0.822). Besides, the area under the curve of WBC plus D dimer was larger, and the predictive value of VTE was higher (AUC=0.802, 95%CI 0.736-0.858). In the sensitivity and specificity analysis, the combination group had the highest specificity (79.78%) (Table 5).

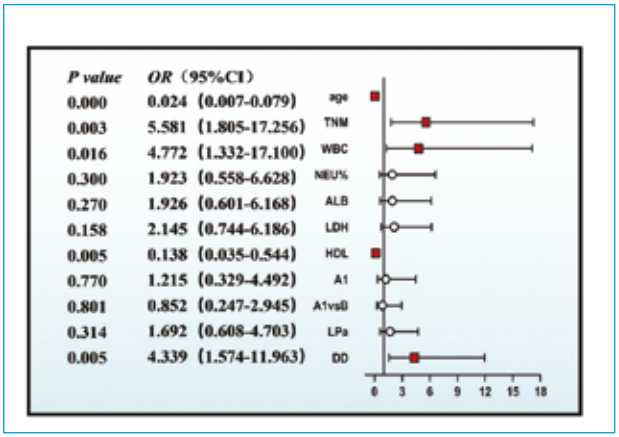

Figure 2: Forest plot of multivariate.

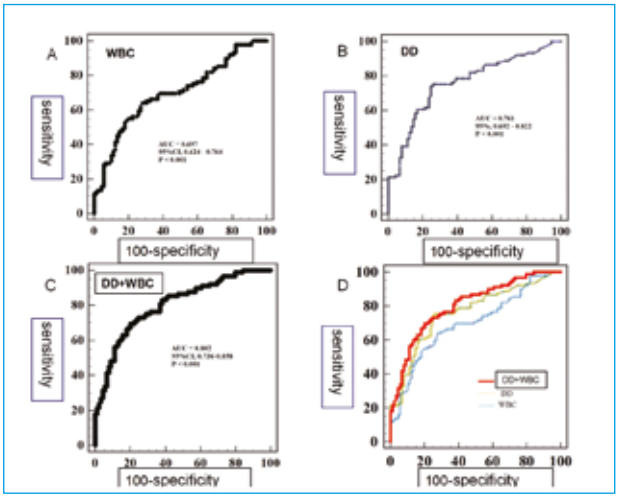

Figure 3: ROC curves of WBC, D-dimer, and combination of the above.

	Sensitivity (%)	specificity (%)	*cut-off*
WBC plus D dimer	69.66	79.78	0.426
WBC	64.04	71.91	7.99
D dimer	75.28	74.16	1.11

Table 5: The sensitivity and specificity of WBC and D dimer and their combination to predict the formation of VTE, respectively.

Discussion

As we set strict inclusion and exclusion criteria and eliminated the interference of many factors, the results from our study could be very representative. We found that the risk of VTE for people younger than 65 was higher than that for people older than 65. This is inconsistent with the result of Khorana et al18, who enrolled 45,872 patients with VTE. Due to the small sample size of our study, and no further stratification analysis for people younger than 65, this may have led to differences in results. We also found that patients with stage IV cancer had a higher risk of VTE, and the risk of VTE was about 5.5 times higher than that of patients with stage I-III,

which is consistent with the conclusion of a recent prospective study[19].

In this study, we revealed that elevated WBC and D-dimer were independent risk factors for lung cancer patients with VTE, and elevated WBC will increase the risk of VTE, which is consistent with the conclusions of Zhang Y et al[20]. Since leukocytes adhere to endothelial cells and platelets, they play an important role in the activation of the coagulation cascade. Excessive activation of leukocytes can cause a systemic procoagulant state, which may lead to increased WBC and increased risk of thrombosis. This study also found that D dimer is an independent risk factor for VTE, and it is a biomarker with high sensitivity and specificity. The value of D dimer in VTE has been reported in the literature[21-23]. Although the cut-off value of D dimer selection is controversial, we found that the increase of D dimer increases the risk of VTE. In the clinics, many patients whose D dimer is slightly higher than the normal value (>0.5 mg/L) are often without VTE. Therefore, 1.44 mg/L is selected as the cutoff value of D dimer in this article. This is based on a previous report[24].

The relationship between blood lipids and the risk of VTE is the focus of this study. There have been some reports on the relationship between HDL and venous thrombosis. Studies have found that elevated HDL is negatively correlated with the risk of VTE[14,25]. However, these studies are limited to tumor-free patients, who usually have risk factors such as cardiovascular and cerebrovascular diseases. In this study, to understand the relationship between thrombosis and blood lipids in tumor patients, we excluded possible influencing factors such as vascular disease and risk factors. We found that in lung cancer patients, HDL (<1 mmol/L) increases the risk of VTE, and low levels of HDL (<1 mmol/L) can be considered as a risk factor for VTE. HDL may be a potential protective factor for lung cancer-related VTE. Previous studies have found that the reduction of HDL levels (≤43 mg/dl) in patients with cancer during chemotherapy increased the risk of VTE for the first time in this patient by three fold[26]. It indirectly shows that the reduction of HDL level is related to the increase of VTE risk, which is consistent with the conclusions of our study. In terms of mechanism, the main function of HDL is the reverse transport of cholesterol, and in this lipid uptake process, it mainly relies on the Class B Type I Scavenger Receptor (SR-BI). SR-BI can mediate the activation of HDL-induced endothelial nitric oxide synthase (eNOS), and its product nitric oxide (NO) has anti-thrombosis and anti-atherosclerotic effects[27]. In a mouse model of deep vein thrombosis, studies have shown that the lack of HDL receptor SR-BI can promote venous thrombosis[28]. HDL can also inhibit vascular inflammation and enhance endothelial function, reduce damage to endothelial cells, and play an anti-thrombotic effect[29]. Therefore, HDL may reduce the risk of VTE through these mechanisms. Considering that the above mechanism is limited to tumor-free research subjects, whether it is consistent in tumor models still needs to be explored. In this study, univariate analysis of APO-A, LPa, and A1/B between the VTE group and the non-VTE group was statistically different, but there was no significant difference in the multivariate analysis. The result of this study is related to the small sample size, and its relationship with VTE risk still needs more clinical studies to confirm. We did not find that CHO and TG are associated with lung cancer-related VTE risk. It may be that the above indicators are affected by the population's age, gender, living habits, genes and environment, and other factors, causing great individual differences.

Given the potential relationship between HDL and the risk of VTE, the preventive use of lipid-lowering drugs may benefit lung cancer patients with VTE. Basic research has found that statins have anti-inflammatory and immunomodulatory effects, and are also related to antithrombotic activity[30]. In tumor-free patients, studies have found that the use of statins could reduce the risk of DVT and PE[31,32]. A meta-analysis33 showed that the use of statins reduced the risks of VTE, DVT, and PE by 32%, 41%, and 30%, respectively. We speculate that the preventive use of statins may have potential benefits for the tumor population and may reduce the risk of VTE, which might be of therapeutic value.

The limitations of this study are only involved in a small sample size of 89 case samples, and the type is a retrospective case-control study. Therefore, it may be better to expand the data volume to further confirm this possible relationship.

Conclusion

In lung cancer patients, elevated WBC and D-dimer were independent risk factors for lung cancer patients with VTE, and elevated WBC and D dimers may increase the risk of VTE. However, higher levels of HDL may decrease the risk of VTE, and HDL is a possible protective factor.

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