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Research Letter

Development and Validation of a Novel Noninvasive Model to Predict Liver Fibrosis Staging in Untreated Patients with Chronic Hepatitis B

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Hepatitis B virus infection represents a major global public health challenge.[1] Chronic hepatitis B (CHB) virus infection is a leading cause of liver fibrosis, a key pathological process that drives the progression of chronic liver disease to cirrhosis. Current clinical guidelines recommend the immediate initiation of antiviral therapy upon detection of significant liver fibrosis in patients with CHB.[2–4] Early-stage fibrosis may be reversible with effective antiviral treatment, whereas advanced fibrosis or cirrhosis shows limited reversibility despite therapy.[5] As such, early identification and staging of liver fibrosis, followed by timely antiviral intervention, are crucial for optimizing the management of CHB and improving long-term patient outcomes.

Liver biopsy remains the gold standard for diagnosing liver fibrosis,[6] but its invasiveness and sampling variability limit its widespread clinical use.[7] In recent decades, significant advancements have been made in noninvasive fibrosis assessment, including transient elastography (TE, e.g., FibroScan), serum biomarkers, and composite fibrosis prediction models. TE demonstrates high diagnostic accuracy for distinguishing significant fibrosis and cirrhosis in chronic hepatitis C and CHB cohorts.[8] However, TE measurements can be affected by obesity, ascites, elevated bilirubin levels, and operator-dependent factors, potentially compromising diagnostic reliability.[8]

Integrating multiple serological markers, such as the aspartate transaminase-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) index,[9,10] with fibrohepatic assessment models has proven to be a valid strategy. However, both APRI and FIB-4 were originally derived from chronic hepatitis C cohorts, and their applicability to patients with CHB remains controversial.[11] Lemoine, *et al*. proposed the gamma-glutamyl transpeptidase-to-platelet ratio (GPR) model for CHB-related fibrosis in 2016, reporting superior diagnostic accuracy compared to APRI and FIB-4.[12] However, a study by Chinese scholars found that its accuracy was not superior to either the APRI or FIB-4 models.[13]

Classic liver fibrosis biomarkers, including laminin, hyaluronic acid (HA), procollagen type III N-terminal peptide, and collagen type IV (CIV), are widely utilized in clinical practice, but their diagnostic accuracy may be confounded by systemic inflammation or concurrent rheumatological conditions.[14,15] Therefore, these markers should be integrated with complementary indicators for a more robust fibrosis assessment. This study aimed to develop a novel noninvasive model incorporating routine serum biomarkers for untreated CHB patients and validate its performance against established models (FIB-4, APRI, and GPR).

A total of 382 treatment-naïve CHB patients who underwent liver biopsy at the First Affiliated Hospital, Zhejiang University School of Medicine, between January 1, 2013, and March 31, 2021, were enrolled. Of these, 258 patients who were hospitalized before October 2018 were included in the derivation cohort, and 124 patients hospitalized in or after October 2018 were included in validation cohort 1. Additionally, 89 eligible treatment-naïve CHB patients who underwent liver biopsy at Sulan (Hangzhou) Hospital between October 1, 2018, and March 31, 2021, were enrolled as validation cohort 2. Among the 471 patients, 146 (31.00%) had significant fibrosis or higher (according to the METAVIR scoring system). The clinical and laboratory characteristics of the patients are shown in Supplementary Table 1.

In the derivation cohort of 258 patients, 94 (36.43%) had significant liver fibrosis. Compared to patients with nonsignificant liver fibrosis (164 patients, 63.57%), those

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Table 1. Logistic regression analysis of factors associated with significant fibrosis in untreated patients with CHB in the derivation cohort

Factors	Univariate			Multivariate		
	B	**OR (95%CI)**	***P***	**B**	**OR (95%CI)**	***P***
PLT (10^9/L)	−0.008	0.992 (0.987–0.997)	0.002	−0.008	0.992 (0.986–0.998)	0.008
PT (s)	0.348	1.416 (0.999–2.008)	0.051			
Albumin (g/L)	−0.095	0.909 (0.854–0.969)	0.003			
Globulin (g/L)	0.085	1.088 (1.017–1.165)	0.015			
A/G	−1.805	0.164 (0.061–0.440)	0.000	−1.438	0.237(0.077–0.734)	0.013
ALT (U/L)	0.006	1.006 (1.002–1.010)	0.006			
AST (U/L)	0.024	1.024 (1.012–1.037)	0.000	0.022	1.022 (1.010–1.034)	<0.001
ChE (U/L)	0.000	1.000 (1.000–1.000)	0.019			
γ-GT (U/L)	0.020	1.020 (1.008–1.033)	0.001			
AFP (ng/ml)	0.053	1.055 (1.007–1.105)	0.024			
HBcAb (S/CO)	0.137	1.146 (1.018–1.291)	0.024			
HA (ng/ml)	0.031	1.032 (1.020–1.043)	0.000	0.029	1.030 (1.017–1.043)	<0.001
PIIINP (ng/ml)	0.038	1.039 (1.015–1.064)	0.002			
CIV (ng/ml)	0.033	1.033 (1.016–1.052)	0.000	0.032	1.033 (1.013–1.053)	0.001

AFP, alpha-fetoprotein; A/G, albumin/globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; ChE, cholinesterase; CI, confidence interval; CIV, collagen IV; γ-GT, γ-glutamyl transpeptidase; HA, hyaluronic acid; HBcAb, HBV core antibody; OR, odds ratio; PIIINP, procollagen type III N-terminal peptide; PLT, platelets; PT, prothrombin time.

with significant liver fibrosis had significantly lower platelet (PLT) counts, plasma albumin levels, albumin/globulin ratios, and cholinesterase levels ($P = 0.002$, $P = 0.003$, $P < 0.001$, and $P = 0.017$, respectively). In contrast, patients with significant liver fibrosis had significantly higher prothrombin times, globulin levels, alanine aminotransferase, aspartate aminotransferase (AST), γ-glutamyl transpeptidase, alpha-fetoprotein, hepatitis B virus core antibody, HA, procollagen type III N-terminal peptide, and CIV levels (all $P < 0.05$). The clinical and laboratory characteristics of the CHB patients in the derivation cohort are shown in Supplementary Table 2.

Building on prior evidence and focusing on readily accessible parameters, statistically significant variables ($P < 0.05$) identified in Supplementary Table 2 were subjected to univariate and multivariable logistic regression analyses to identify independent predictors of significant liver fibrosis (F2-4) in the CHB derivation cohort. Multivariable analysis confirmed that PLT, albumin/globulin ratio, AST, HA, and CIV were independent indicators of significant liver fibrosis (all $P < 0.05$; Table 1). Subsequently, four parameters (PLT, AST, HA, CIV) with $P < 0.01$ were integrated to construct a novel diagnostic model (FIBROSIS). The formula is as follows:

$$\text{FIBROSIS} = \frac{\text{AST (U/L)} \times \text{HA (ng/mL)} \times \text{CIV (ng/mL)}}{\text{PLT } (10^9/\text{L}) \times 1000}$$

The performance of the FIBROSIS staging of liver fibrosis was as follows: an area under the receiver operating characteristic curve (AUROC) of 0.821 (95% CI 0.768–0.865) for the prediction of significant fibrosis, with a sensitivity of 84.04% and specificity of 68.29%, using an optimal cutoff value of 0.19; an AUROC of 0.737 (95% CI 0.679–0.790) for advanced fibrosis, with a sensitivity of 76.32% and specificity of 64.09%, using an optimal cutoff value of 0.24; and an AUROC of 0.825 (95% CI 0.772–0.869) for cirrhosis, with a sensitivity of 87.50% and specificity of 61.60%, using an optimal cutoff value of 0.26 (Table 2). For the prediction of significant fibrosis (F2-4), the AUROC of the FIBROSIS model was significantly greater than that of APRI (0.749 [0.691–0.800], $P = 0.0034$), FIB-4 (0.677 [0.616–0.733], $P < 0.001$), and GPR (0.692 [0.632–0.748], $P < 0.0001$) (Fig. 1A) (Supplementary Table 3). For the prediction of advanced fibrosis (F3-4), the AUROC of FIBROSIS was significantly greater than that of APRI (0.664 [0.602–0.721], $P = 0.0480$), FIB-4 (0.622 [0.559–0.681], $P = 0.0164$), and GPR (0.642 [0.580–0.700], $P = 0.0331$) (Fig. 1B) (Supplementary Table 3). For the prediction of cirrhosis (F4), the AUROC of FIBROSIS was significantly greater than that of GPR (0.636 [0.574–0.695], $P = 0.0324$) and comparable to that of APRI (0.713 [0.654–0.767], $P = 0.0648$) and FIB-4 (0.680 [0.619–0.736], $P = 0.0716$) (Fig. 1C) (Supplementary Table 3).

In validation cohort 1, for the diagnosis of significant fibrosis (F2-4), the AUROC of FIBROSIS was 0.849 (0.773–0.907), which was greater than that of FIB-4 (0.650 [0.559–0.733], $P = 0.0013$) and comparable to those of APRI (0.828 [0.750–0.890], $P = 0.6359$) and GPR (0.780 [0.697–0.849], $P = 0.2230$) (Fig. 1D) (Supplementary Table 3). Using the optimal cutoff value of 0.19 determined in the training set, the sensitivity and specificity of FIBROSIS for predicting significant fibrosis were 80.77% and 65.31%, respectively. For the diagnosis of advanced fibrosis (F3-4), the AUROC of FIBROSIS was 0.866 (0.793–0.921), which was greater than that of FIB-4 (0.652 [0.561–0.735], $P = 0.0066$) and comparable to those of APRI (0.815 [0.735–0.879], $P = 0.2618$) and GPR (0.787 [0.704–0.855], $P = 0.3671$) (Fig. 1E) (Supplementary Table 3). Using the optimal cutoff value of 0.24 determined in the training set, the sensitivity and specificity of FIBROSIS for predicting advanced fibrosis were 81.82% and 75.22%, respectively. For the diagnosis of cirrhosis (F4), the AUROC of FIBROSIS was 0.923 (0.861–0.963), which was greater than that of APRI (0.766 [0.681–0.837], $P = 0.0018$) and GPR (0.745 [0.659–0.819], $P = 0.0024$), and comparable to that of FIB-4 (0.668 [0.578–0.750], $P = 0.0777$) (Fig. 1F) (Supplementary Table 3). Using the optimal cutoff value of 0.26 determined in the training set, the sensitivity and specificity of FIBROSIS for predicting cirrhosis

Table 2. Performance of FIBROSIS and other non-invasive models in diagnosing liver fibrosis stage in the derivation cohort and validation cohort

Models	AUROC (95% CI)	Cut-off values	Sensitivity/ Specificity (%)	PPV/NPV (%)	PLR/NLR	Youden	*P*
Derivation cohort							
Significant fibrosis (F2–4)							
FIBROSIS	0.821 (0.768–0.865)	0.19	84.04/68.29	60.3/88.2	2.65/0.23	0.5234	<0.0001
APRI	0.749 (0.691–0.800)	0.36	84.04/59.76	54.5/86.7	2.09/0.27	0.4380	<0.0001
FIB-4	0.677 (0.616–0.733)	1.10	68.83/69.51	54.5/77.0	2.09/0.52	0.3334	<0.0001
GPR	0.692 (0.632–0.748)	0.28	59.57/71.34	54.4/75.5	2.08/0.57	0.3092	<0.0001
Advanced fibrosis (F3–4)							
FIBROSIS	0.737 (0.679–0.790)	0.24	76.32/64.09	26.9/94.0	2.13/0.37	0.4041	<0.0001
APRI	0.664 (0.602–0.721)	0.42	73.68/56.36	22.6/92.5	1.69/0.47	0.3005	0.0002
FIB-4	0.622 (0.559–0.681)	1.10	63.16/60.91	21.8/90.5	1.62/0.60	0.2407	0.0113
GPR	0.642 (0.580–0.700)	0.28	63.16/64.09	23.3/91.0	1.76/0.57	0.2725	0.0037
Cirrhosis (F4)							
FIBROSIS	0.825 (0.772–0.869)	0.26	87.50/61.60	6.8/99.4	2.28/0.20	0.4910	<0.0001
APRI	0.713 (0.654–0.767)	0.70	62.50/79.60	8.9/98.5	3.06/0.47	0.4210	0.0166
FIB-4	0.680 (0.619–0.736)	1.26	75.00/68.80	7.1/98.9	2.40/0.36	0.4380	0.1227
GPR	0.636 (0.574–0.695)	0.32	62.50/66.40	5.6/98.2	1.86/0.56	0.2890	0.2337
Validation cohort 1							
Significant fibrosis (F2–4)							
FIBROSIS	0.849 (0.773–0.907)	0.19	80.77 /65.31	38.18/92.75	2.33/0.29	0.4608	<0.0001
APRI	0.828 (0.750–0.890)	0.36	76.92/73.47	43.48/92.31	2.90/0.31	0.5039	<0.0001
FIB-4	0.650 (0.559–0.733)	1.10	50.00/66.33	28.26/83.33	1.49/0.75	0.1633	0.0124
GPR	0.780 (0.697–0.849)	0.28	65.38/75.51	41.46/89.16	2.67/0.46	0.4089	<0.0001
Advanced fibrosis (F3–4)							
FIBROSIS	0.866 (0.793–0.921)	0.24	81.82/75.22	24.32/97.70	3.30/0.24	0.5704	<0.0001
APRI	0.815 (0.735–0.879)	0.42	81.82/74.34	25.00/97.67	3.19/0.24	0.5616	<0.0001
FIB-4	0.652 (0.561–0.735)	1.10	54.55/64.60	13.04/93.59	1.54/0.70	0.1915	0.0835
GPR	0.787 (0.704–0.855)	0.28	81.82/87.10	21.95/97.59	6.34/0.21	0.6892	<0.0001
Cirrhosis (F4)							
FIBROSIS	0.923 (0.861–0.963)	0.26	100.00/75.63	14.71/100.00	4.10/0.00	0.7563	<0.0001
APRI	0.766 (0.681–0.837)	0.70	60.00/70.59	7.89/97.67	2.04/0.57	0.3059	<0.0001
FIB-4	0.668 (0.578–0.750)	1.26	40.00/76.47	6.67/96.81	1.70/0.78	0.1647	0.2691
GPR	0.745 (0.659–0.819)	0.32	60.00/75.63	9.38/97.83	2.46/0.53	0.3563	0.0004
Validation cohort 2							
Significant fibrosis (F2–4)							
FIBROSIS	0.796 (0.697–0.874)	0.19	46.15/85.71	57.14/79.41	3.11/0.63	0.3186	<0.0001
APRI	0.682 (0.574–0.776)	0.36	50.00/71.43	41.94/77.59	1.75/0.70	0.2143	0.0080
FIB-4	0.617 (0.508–0.718)	1.10	46.15/71.43	40.00/76.27	1.62/0.75	0.1758	0.0740
GPR	0.585 (0.475–0.688)	0.28	38.46/69.84	34.48/66.67	1.28/0.88	0.0830	0.2200
Advanced fibrosis (F3–4)							
FIBROSIS	0.849 (0.757–0.916)	0.24	66.67/84.88	13.33/98.65	4.41/0.39	0.5155	0.0173
APRI	0.783 (0.683–0.863)	0.42	50.00/74.42	8.33/98.46	1.95/0.67	0.2442	0.0013
FIB-4	0.655 (0.547–0.753)	1.10	33.33/66.28	3.33/89.47	0.99/1.01	−0.3900	0.3330
GPR	0.818 (0.722–0.892)	0.28	66.67/68.60	6.90/98.33	2.12/0.49	0.3527	0.0001

APRI, aspartate transaminase to platelet ratio index; AUROC, area under the receiver operating characteristic curve; FIB-4, Fibrosis-4; FIBROSIS, aspartate aminotransferase, hyaluronic acid and collagen IV to platelet ratio index; GPR, gamma-glutamyl transpeptidase to platelet ratio index; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

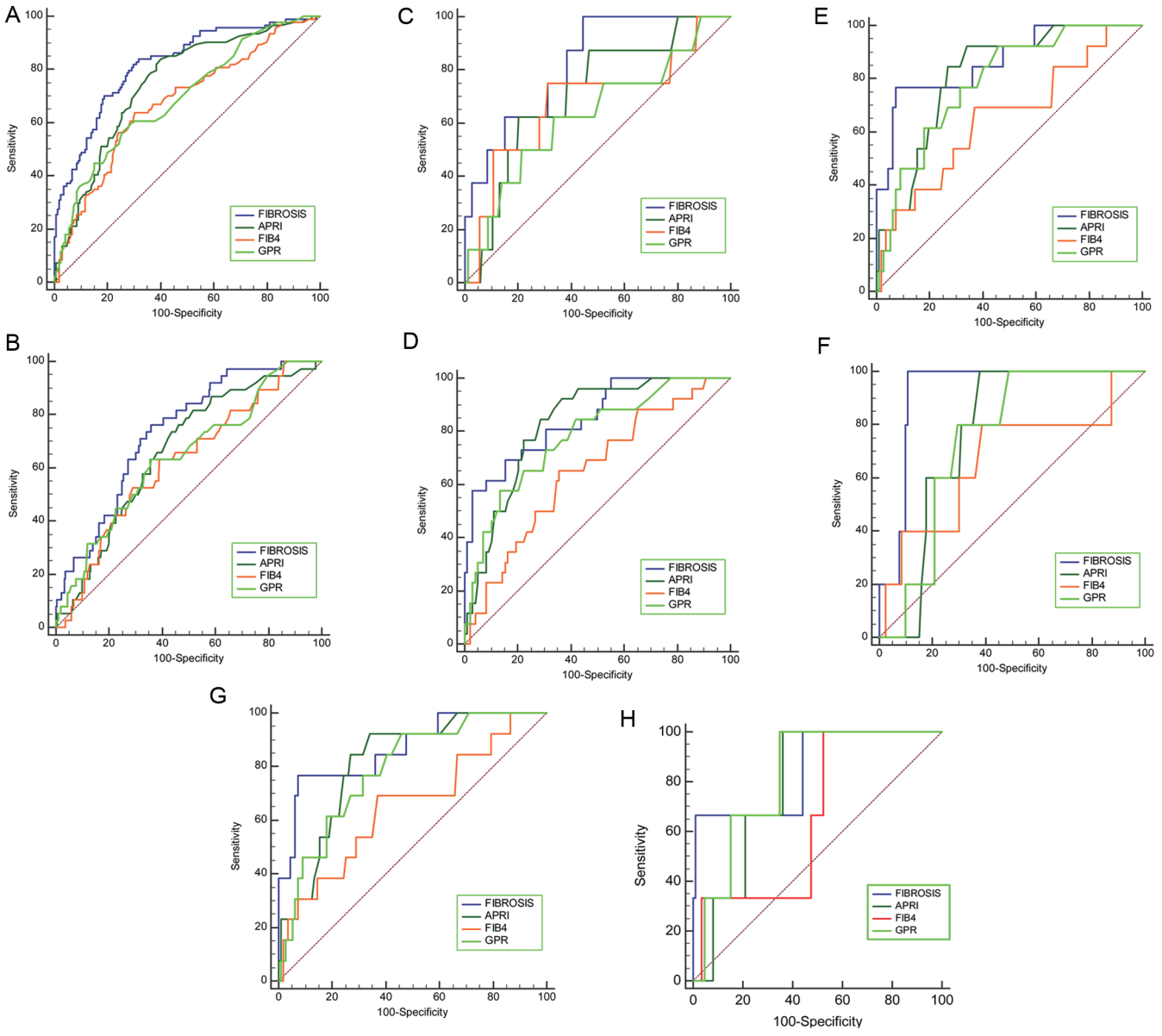

Fig. 1. Performance of FIBROSIS and other models in differentiating significant fibrosis, advanced fibrosis, and cirrhosis in the derivation cohort (A–C), validation cohort 1 (D–F), and validation cohort 2 (G–H). APRI, aspartate transaminase to platelet ratio index; FIB-4, Fibrosis-4; GPR, gamma-glutamyl transpeptidase to platelet ratio index; FIBROSIS, aspartate aminotransferase, hyaluronic acid and collagen IV to platelet ratio index.

were 100% and 75.63%, respectively.

To verify the reliability and applicability of the model, we also screened a separate validation cohort (validation cohort 2) from other centers (Shulan (Hangzhou) Hospital). In validation cohort 2, there were no patients (0.00%) with F4. Therefore, we only tested the performance of FIBROSIS for significant fibrosis and advanced fibrosis. The AUROCs of FIBROSIS for the diagnosis of significant fibrosis (F2-4) and advanced fibrosis were 0.796 (0.697–0.874) and 0.849 (0.757–0.916), respectively, which were either greater than or comparable to those of APRI, FIB-4, and GPR (Table 2, Supplementary Table 3, Fig. 1G and H).

In conclusion, we developed a novel model (FIBROSIS) based on four routine indicators (AST, PLT, HA, CIV), eliminating the need for specialized equipment and facilitating straightforward clinical implementation. Through internal and external cohort validation, the FIBROSIS model demonstrated high accuracy in predicting liver fibrosis in untreated CHB patients, particularly for those with significant fibrosis (F2-4), overcoming the limited generalizability of single-center models. The time-splitting strategy employed effectively mimics real-world data flow, ensuring robust clinical applicability. Consequently, this model offers a non-invasive alternative to liver biopsy for fibrosis prediction in untreated CHB populations.

However, this study has several limitations. First, the retrospective design requires validation through prospective cohorts. Second, although the validation cohort included patients from two centers, the limited sample size from the secondary center resulted in the absence of stage F4

cases in validation cohort 2. Third, the extended enrollment period (January 2013 to March 2021) introduced potential systematic biases due to evolving diagnostic methodologies and advances in antiviral treatments. Fourth, FibroScan data availability was insufficient in the small subgroup of untreated CHB patients, precluding direct comparison with the proposed model, a critical aspect for subsequent refinement.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study design (YY, JH), data collection (FG, XZ, GY, LJ), data analysis (FG, HJ, HG), liver histological section analysis (WZ, XW), and manuscript writing (JH, XZ, ZZ, YY). All authors reviewed and approved the final version and publication of the manuscript.

Ethics statements

This study was approved by the medical ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine, and conforms to the ethical guidelines of the Helsinki Declaration as revised in 2024 (IIT20240534A). Informed consent was waived because this was a retrospective study, and the data was obtained from existing electronic medical records. It was also approved by the medical ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine.

Data sharing statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author: anonymized dataset of the Study is available to Editors, Reviewers and Readers upon request to the corresponding author.

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