

Clinical Implications of Alanine Transaminase Level in the Diagnostic Accuracy of Alpha-Fetoprotein for Predicting Hepatocellular Carcinoma in Patients with Hepatitis B Infection

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Abstract

Background Abnormally elevated AFP level is often observed in patients with chronic hepatitis infections without evident of (hepatocellular carcinoma) HCC. Our study aimed to investigate the influence of alanine transaminase (ALT) on the accuracy of alpha-fetoprotein (AFP) for detecting HCC.

Methods This retrospective study recruited 799 patients with HCC, cirrhosis and chronic hepatitis due to hepatitis B infection and healthy adults between July 2017 and January 2019. Comparisons of the area under the receiver-operating curves (AUCs) for detecting HCC in different ALT levels were calculated.

Results Serum ALT and gamma-glutamyl transferase level were significantly associated with elevated AFP in patients without HCC. The AUC of AFP was higher in patients with $ALT \leq 2$ upper limit of normal (ULN) than in patients with $ALT > 2ULN$ (0.806 vs 0.611, $P < 0.001$). Nevertheless, there was not significant differences in the AUCs of AFP/(ALT×Aspartate aminotransferase(AST)) in patients with $ALT \leq 2$ ULN and with $ALT > 2ULN$ (0.769 vs 0.769, $P = 0.68$). AFP/(ALT×AST) was better than AFP in patients with $ALT > 2ULN$ for detecting HCC ($P < 0.001$).

Conclusions Higher ALT level might impair the accuracy of AFP for diagnosing HCC. AFP tests showed better accuracy in patients with $ALT \leq 2$ ULN whereas AFP/(ALT×AST) ratio was recommended in patients with elevated ALT level.

Background

Hepatocellular carcinoma (HCC) is considered as the fifth most common malignancies in the world with a high mortality rate[1], and it was estimated that half of the HCC cases and deaths occurred in China[2, 3]. The epidemiological observation suggests hepatitis B viral infection is a potential risk factor for HCC[4, 5]. Therefore, cancer screening for target population and early diagnosis of HCC is essential to improve life expectancy and reduce mortality.

Among serum tumor markers, alpha-fetoprotein (AFP) is the most widely used serological marker for HCC evaluation[6]. However, the accuracy of AFP for HCC detection has been intensely debated for relative low accuracy[7–9]. Indeed, the updated American Association for the Study of Liver Diseases (AASLD) guidelines currently exclude AFP from surveillance testing and use ultrasonography as the optimal option for the detection of early HCC[10].

Numerous data have shown the non-specific finding of significantly high serum AFP level in patients with chronic liver disease and cirrhosis[6, 11]. There have been case reports with regard to abnormally elevated AFP level in patients with chronic hepatitis B or C infections without evidence of HCC and elevated serum AFP level decreased in response to antiviral therapy[12–14]. Such results might explain that abnormal elevation of AFP level can be due to hepatic inflammation and viral replication. However, data was scarce about what factors lead to abnormal increase of AFP level in patients with liver disease without developing HCC. Several studies have shown that serum alanine transaminase (ALT) level was

significantly associated with elevated AFP in patients without HCC[15–18]. A recent study illustrated that the diagnostic performance of the novel index $\text{AFP}/[\text{ALT} \times \text{Aspartate aminotransferase}(\text{AST})]$ was superior to that of AFP for HCC[19]. Hence, we hypothesize that increased ALT level might impair the diagnostic accuracy of AFP for the detection of HCC.

Therefore, this retrospective study was aimed to explore the influence of ALT level on the diagnostic accuracy of AFP for the detection of HCC in comparison with $\text{AFP}/(\text{ALT} \times \text{AST})$ ratio.

Methods

Study design and patients

This was a retrospective study conducted at the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between July 2017 and January 2019. Patients with liver disease due to hepatitis B viral infection (including HCC group, group with cirrhosis and group with chronic hepatitis B) and normal health adults (for normal control group) were retrospectively recruited. The exclusion criteria of the study were as follows: (a) had a history of antiviral therapy at study entry as such therapy might have an impact on ALT and AFP level and affect study results; (b) had previous history of liver transplantation; (c) were younger than 18 years; (d) combined with other liver disease (autoimmune liver disease, alcoholic liver disease, non-alcoholic fatty liver disease, et al.); (e) had previous history of tumor treatment for HCC (surgery, ablation therapy or chemoradiotherapy); (f) unavailable AFP value.

The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Informed written consent was obtained from all recruited patients.

Clinical Diagnostic Criteria

The HCC diagnosis in the study was confirmed according to the European Association for the Study of the Liver Clinical Practice guidelines[4]. Newly developed HCC cases were diagnosed by histological findings or at least one positive imaging technique (contrast-enhanced CT, contrast-enhanced MRI or CEUS) for nodules of ≥ 1 cm in diameter for high-risk individuals.

Chronic hepatitis B viral infection was diagnosed for the positive findings of hepatitis B surface antigen for at least 6 months. Cirrhosis was diagnosis based on the clinical, biochemical, ultrasonic findings or biopsy results, as described in previous studies. Normal healthy adults were confirmed without liver disease according to serological and ultrasonic results.

Measurements Of Afp, Alt And Ast

The enrolled patients were required to over-night fasted and all serum samples were collected and measured in the morning. Serum levels of AFP were measured using electrochemiluminescence (Cobas

E601, Roche, Inc., Germany) with the normal reference value of 0–7 ng/ml and an upper limit of detection of 1210 ng/ml. Serum levels of ALT and AST were measured using biochemical rate-assay (Hitachi 7600, Japan). Normal ALT level was interpreted as ≤ 35 U/L.

All serum samples tests were performed by two experience inspectors (J.C. and Z.L. with experience of > 4 years in clinical laboratory analysis).

Statistical analysis

Statistical analyses of the study were performed using SPSS, version 19.0 (SPSS Inc., United States) and Medcalc, version 12.3 (MedCalc Software bvba, Ostend, Belgium).

Continuous variables were presented as median (interquartile range, 25th–75th percentile) for abnormal distribution data or mean \pm standard deviation for normal distribution data. Categorical variables were expressed as number (percentage). Comparisons between groups were assessed using the Student t test or the Mann-Whitney test for continuous variables or the χ^2 or Fisher test for categorical variables when appropriate. The correlation of two factor analysis was assessed with Spearman's rank correlation coefficient.

In order to determine factors associated abnormal elevated serum AFP level (> 20 ng/ml) among patients with hepatitis B without developing HCC, univariable and multivariable logistic analysis were conducted. Only the factors significantly associated with elevated serum AFP level in patients without HCC ($P < 0.05$) in univariable analysis could enter in the multivariable logistic analysis. The multivariable logistic was processed using forward stepwise regression method. The estimated odds ratio (OR) with its 95% confidence interval (CI) was presented in the study results.

The diagnostic performances of serum AFP and AFP/(ALT \times AST) ratio for the detection of HCC were evaluated using the receiver-operating characteristic (ROC) curves (AUCs). Comparison of AUCs of different parameters for diagnosis of HCC were assessed with DeLong tests. The optimal cutoff value is determined by the best Youden's index, which is calculated according to the following formula: Youden's index = sensitivity + specificity – 1. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and their 95% CIs were shown in the Table.

For all analysis, all statistical tests were two-sided and P value < 0.05 was regarded as statistically significant.

Results

Clinical Characteristics

The baseline characteristics of the enrolled patients were presented in Table 1. Of 902 patients recruited at the initial stage of the study, 799 patients were eligible for the study, including 240 patients with HCC

(HCC group), 153 patients with cirrhosis (cirrhosis group), 248 patients with chronic hepatitis B (chronic hepatitis group) and 158 healthy adults (healthy control group). Of the enrolled patients, there were 637 male patients (79.7%, 637/799) and the median age was 46.0 years old (interquartile range: 36.0–56.0 years old). P values for comparisons between different groups was presented in Table 1. AFP level and AFP/(ALT × AST) ratio in the HCC group was significantly higher than that in other groups (all P values < 0.001). The flow chart of the study population was shown in Fig. 1.

Table 1
Baseline demographic data of the study population (n = 799).

Variable	HCC (n = 240)	Cirrhosis (n = 153)	Chronic Hepatitis (n = 248)	Healthy Group (n = 158)	P ₁ value	P ₂ value	P ₃ value
Demographic							
Age (years)	53.0 (44.0–62.0)	53.0 (47.0–62.0)	42.0 (34.0–49.0)	34.0 (28.0–45.0)	0.26	< 0.001	< 0.001
Sex, male	221 (92.1%)	110 (71.9%)	197 (79.4%)	109 (69.0%)	< 0.001	< 0.001	< 0.001
Hematological data							
HGB (g/L)	139.0 (127.0–151.0)	117.0 (97.0–134.0)	142.0 (128.0–153.5)	151.0 (136.0–158.0)	< 0.001	0.24	< 0.001
PLT (10 ⁹ /L)	169.9 (120.0–224.0)	89.0 (63.5–126.5)	180.0 (139.0–229.0)	251.0 (217.0–285.5)	< 0.001	0.08	< 0.001
PT (s)	13.8 (13.3–14.5)	16.2 (14.7–18.5)	14.4 (13.3–16.9)	12.9 (12.4–13.3)	< 0.001	< 0.001	< 0.001
Liver function tests							
AST (IU/L)	32.0 (25.0–48.8)	49.0 (32.5–74.0)	47.5 (27.0–213.5)	19.0 (16.0–22.0)	< 0.001	< 0.001	< 0.001
ALT (IU/L)	34.5 (24.0–49.8)	35.0 (23.0–56.5)	65.5 (27.0–413.8)	19.0 (13.8–27.0)	0.43	< 0.001	< 0.001

Data were presented as median (interquartile range, 25th–75th percentile) or number (percentage).

HCC, hepatocellular carcinoma; HGB, hemoglobin; PLT, platelet count; PT, prothrombin time; AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

For convenience of representation, the value of AFP/(ALT × AST) was 1000 times of the actual value.

P₁ value was given for the comparison of HCC and cirrhosis group; P₂ value was given for the comparison of HCC and chronic hepatitis group; P₃ value was given for the comparison of HCC and healthy control group.

Variable	HCC (n = 240)	Cirrhosis (n = 153)	Chronic Hepatitis (n = 248)	Healthy Group (n = 158)	P ₁ value	P ₂ value	P ₃ value
GGT (IU/L)	55.5 (32.4–98.0)	53.0 (35.0–136.0)	47.0 (22.0–161.0)	22.0 (16.0–34.0)	0.42	0.20	< 0.001
ALP (IU/L)	85.0 (67.0–117.3)	104.0 (81.0–147.0)	86.5 (67.0–123.3)	60.0 (48.0–68.0)	< 0.001	0.88	< 0.001
Tumor markers							
AFP (ng/mL)	18.6 (4.8–200.0)	5.1 (2.7–12.1)	4.6 (1.9–36.5)	2.8 (2.0–3.9)	< 0.001	< 0.001	< 0.001
AFP/(ALT × AST) (10 ⁻³)#	17.6 (4.3–122.0)	3.3 (1.3–8.2)	1.7 (0.3–4.6)	8.6 (3.7–14.1)	< 0.001	< 0.001	< 0.001
Data were presented as median (interquartile range, 25th–75th percentile) or number (percentage).							
HCC, hepatocellular carcinoma; HGB, hemoglobin; PLT, platelet count; PT, prothrombin time; AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.							
# For convenience of representation, the value of AFP/(ALT × AST) was 1000 times of the actual value.							
P ₁ value was given for the comparison of HCC and cirrhosis group; P ₂ value was given for the comparison of HCC and chronic hepatitis group; P ₃ value was given for the comparison of HCC and healthy control group.							

Factors associated with elevated serum AFP level in patients with cirrhosis and chronic hepatitis B groups

Table 2 showed the clinical and biochemical parameters correlated with elevated serum AFP level (> 20 ng/ml) in patients with cirrhosis and chronic hepatitis B. Univariable analysis showed that male gender (P = 0.01), ALT level (P < 0.001), AST level (P < 0.001), alkaline phosphatase level (P = 0.045), gamma-glutamyl transferase level (P < 0.001) and prothrombin time (P = 0.02) were significantly associated with elevated serum AFP level (> 20 ng/ml) in patients with hepatitis B without developing HCC. In multivariable analysis, only serum ALT level (P < 0.001) and gamma-glutamyl transferase level (P = 0.02) were significantly associated with abnormal elevated serum AFP level in patients with hepatitis B. Increased serum ALT level was significantly correlated with abnormal elevated AFP level (Rs = 0.395, P < 0.001) using Spearman's rank correlation coefficient.

Table 2

Univariable and multivariable logistic regression analysis of factors associated with elevated AFP (≥ 20 ng/mL) in cohort with chronic hepatitis B and cirrhosis (n = 401)

Variable	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.00 (0.98, 1.02)	0.95		
Sex, male	2.52 (1.25, 5.11)	0.01		
AST (IU/L)	1.01 (1.00, 1.01)	<0.001		
ALT (IU/L)	1.01 (1.00, 1.01)	<0.001	1.00 (1.00, 1.01)	< 0.001
GGT (IU/L)	1.01 (1.00, 1.01)	<0.001	1.00 (1.00, 1.00)	0.02
ALP (IU/L)	1.01 (1.00, 1.01)	0.045		
HGB (g/L)	1.00 (1.00, 1.01)	0.43		
PLT (10^9 /L)	1.00 (1.00, 1.00)	0.09		
PT (s)	1.08 (1.02, 1.14)	0.02		

AFP, alpha fetoprotein; OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; HGB, hemoglobin; PLT, platelet count; PT, prothrombin time.

Serum AFP level in patients with cirrhosis and chronic hepatitis B with different serum ALT level

Table 3 presented serum AFP level in cirrhosis and chronic hepatitis B group with different serum ALT levels. The median value of serum AFP level was 4.0 ng/ml, 4.2 ng/ml, 38.6 ng/ml and 43.2 ng/ml in cirrhosis group with normal ALT level, 1 upper limit of normal (ULN) < ALT level \leq 2ULN, 2 ULN < ALT level \leq 5ULN and ALT level > 5ULN, respectively. The median value of serum AFP level in cirrhosis group with serum ALT level > 2ULN was significantly higher than those with serum ALT level \leq 2ULN (P < 0.001) whereas there was not significant difference between the median value of AFP level in cirrhosis group with normal serum ALT level and those with 1ULN < serum ALT level \leq 2ULN (P = 0.73).

Table 3

Values of serum AFP (ng/ml) level in patients with chronic hepatitis B and cirrhosis (n = 401) with different alanine aminotransferase (ALT) levels

ALT level (IU/L)	Cirrhosis (n = 153)	Chronic Hepatitis (n = 248)
Normal	4.0 (2.6–8.2) (n = 78)	2.1 (1.5–3.5) (n = 86)
1–2 × ULN	4.2 (2.1–7.5) (n = 48)	3.2 (1.6–7.2) (n = 44)
2–5 ULN	38.6 (8.5–94.5) (n = 19)	6.6 (2.3–80.9) (n = 36)
> 5 × ULN	43.2 (20.5-149.1) (n = 8)	42.7 (13.7-113.9) (n = 82)
Data were presented as median (interquartile range, 25th–75th percentile).		
AFP, alpha fetoprotein; ALT, alanine aminotransferase; ULN, upper limit of normal.		

For chronic hepatitis B group, the median value of serum AFP level was 2.1 ng/ml, 3.2 ng/ml, 6.6 ng/ml and 42.7 ng/ml in chronic hepatitis group with normal ALT level, 1 upper limit of normal (ULN) < ALT level \leq 2ULN, 2 ULN < ALT level \leq 5ULN and ALT level > 5ULN, respectively. Similarly, the median value of serum AFP level in chronic hepatitis B group with serum ALT level > 2ULN was significantly higher than those with serum ALT level \leq 2ULN ($P < 0.001$) whereas there was not significant difference between the median value of AFP level in chronic hepatitis B group with normal serum ALT level and those with IULN < serum ALT level \leq 2ULN ($P = 0.05$).

Performance of serum AFP and AFP/(ALT × AST) ratio for the diagnosis of HCC in patients with different serum ALT levels

Comparison of accuracy of AFP and AFP/(ALT × AST) ratio for detecting HCC

The performance of AFP and AFP/(ALT × AST) ratio for diagnosis of HCC in patients with different ALT levels are shown in Table 4.

Table 4

Performance of AFP and AFP/(ALT × AST) ratio for diagnosis of HCC in patients with different ALT levels

Parameter	Cutoff	AUC (95% CI)	P value [#]	Sensitivity	Specificity	LR+	LR-
AFP (ng/ml)			< 0.001				
Total cohort	7.8	0.725 (0.691–0.756)		0.65 (0.58–0.71)	0.72 (0.68–0.75)	2.27 (2.0–2.5)	0.49 (0.4–0.6)
Cohort with ALT ≤ 2 × ULN	7.8	0.806 (0.771–0.837)		0.63 (0.56–0.70)	0.88 (0.84–0.91)	5.07 (4.5–5.7)	0.42 (0.3–0.6)
Cohort with ALT > 2 × ULN	88.3	0.611 (0.535–0.683)		0.52 (0.33–0.71)	0.76 (0.68–0.83)	2.15 (1.5–3.1)	0.64 (0.4–1.0)
AFP/(ALT × AST) (10 ⁻³) ^{&}			0.68				
Total cohort	18.0	0.769 (0.737–0.799)		0.50 (0.44–0.57)	0.91 (0.88–0.93)	5.32 (4.7–6.1)	0.55 (0.4–0.7)
Cohort with ALT ≤ 2 × ULN	28.3	0.745 (0.707–0.780)		0.46 (0.40–0.53)	0.95 (0.93–0.97)	9.92 (8.6–11.5)	0.56 (0.3–0.9)
Cohort with ALT > 2 × ULN	5.6	0.769 (0.700–0.829)		0.59 (0.39–0.77)	0.86 (0.79–0.91)	4.13 (3.0–5.6)	0.48 (0.3–0.9)
AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; AUC, area under the receiver operating characteristic curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; ULN, upper limit of normal.							
^{&} For convenience of representation, the value of AFP/(ALT × AST) was 1000 times of the actual value.							
[#] P value was calculated for comparison of AUCs in patients with ALT ≤ 2 × ULN and those with ALT > 2 × ULN.							

In the total population (n = 799), the performance of AFP (AUC: 0.725; 95%CI 0.691–0.756) was significantly lower than that of AFP/(ALT × AST) (AUC: 0.769; 95%CI 0.737–0.799) in the diagnosis of HCC (P < 0.001). In patients with serum ALT level ≤ 2ULN, AFP showed better diagnostic accuracy compared to AFP/(ALT × AST) ratio (P < 0.001). In contrast, in patients with ALT level > 2ULN, the diagnostic performance of AFP/(ALT × AST) ratio is significantly higher than that of AFP for HCC (P < 0.001).

Comparison of accuracy of parameters in different serum ALT levels

Comparisons of AUCs showed that the AUC of serum AFP decreased significantly from 0.806 (95% CI 0.771–0.837) in patients with serum ALT level \leq 2ULN to 0.611 (95% CI 0.535–0.683) in patients with serum ALT level $>$ 2ULN ($P < 0.001$). Nevertheless, there was not significant difference between the AUCs of AFP/(ALT \times AST) ratio in patients with different ALT level (0.769 vs 0.769, respectively; $P = 0.68$).

Discussion

High level of serum AFP level is highly suspicious of hepatocellular carcinoma. However, abnormal elevated serum AFP level was also found in patients with chronic hepatitis B or cirrhosis without evidence of HCC[6, 11, 20]. The present study illustrated that serum ALT level has an independent effect on serum AFP level and elevated ALT level might impair the diagnostic performance of AFP tests for detection of HCC. Our study found that the diagnostic performance of AFP tests was superior in patients with ALT level \leq 2ULN (AUC 0.806; 95% CI 0.771–0.837) than in patients with ALT level $>$ 2ULN (AUC 0.611; 95% CI 0.535–0.683; $P < 0.001$) (Table 4). In patients with ALT level $>$ 2ULN, AFP/(ALT \times AST) ratio (AUC 0.769; 95% CI 0.700–0.829) was better than AFP tumor ($P < 0.001$) marker in diagnosing HCC, with its sensitivity and specificity significantly increasing.

The main findings of the current study are in agreement with previous studies[15, 21]. The prevalence of abnormal elevated AFP levels in patients with chronic hepatitis C is about 10–43% in Western countries[22–24]. Previous studies have confirmed that serum AFP level decreased or increased in parallel with the levels of serum ALT level in non-cancerous liver diseases[15–18]. Abnormal elevated AFP levels were found to decrease in response to antiviral therapy[12], suggesting that hepatic inflammation and viral replication were potential confounding factors for AFP tests in detection for HCC. However, to date, the underlying mechanism of the association between AFP level and hepatic inflammation is still poorly understood, which need to be further investigated in future studies. Our findings suggest that the measurement of AFP is not sufficient to detect HCC in patients with ALT level $>$ 2ULN and dynamic observation of serum AFP level during antiviral treatment is essential to avoid misleading result of AFP tests for diagnosing HCC.

In the present study, we also compared the diagnostic value of AFP marker and AFP/(ALT \times AST) ratio in diagnosing HCC. Liu X. et al first used this novel index AFP/(ALT \times AST) ratio in their study and found that the diagnostic value of AFP/(ALT \times AST) ratio was significantly better than that of AFP, with AUC up to 0.853 (95% CI 0.818–0.887) and 0.825 (95% CI 0.782–0.868) for differentiating HCC from non-HCC patients and from cirrhosis patients, respectively[19]. Our current data also illustrated that the diagnostic value of the index AFP/(ALT \times AST) ratio was superior to that of serum AFP marker for detecting HCC, especially in patients with elevated serum ALT level. Notably, there was not significant difference of the diagnostic performance of AFP/(ALT \times AST) ratio in patients with different ALT level, suggesting AFP/(ALT \times AST) ratio could avoid the influences of hepatic inflammatory factors in detecting HCC.

However, the diagnostic efficacy of this new index for diagnosing HCC in patients with various liver disease need to be validated in future studies.

Unique features of our current study are the focus on the impact of serum ALT level on the diagnostic performance of AFP tests for detection of HCC. The study specifically analyzed the value of serum AFP level in patients with chronic hepatitis B and cirrhosis according to different ALT level, illustrating ALT > 2ULN might significantly affect AFP. On the other hand, our data strongly suggest that AFP is a good test for detection of HCC in patients with hepatitis B with ALT level \leq 2ULN. And the index AFP/(ALT \times AST) ratio was better than AFP for detection of HCC in patients with obvious hepatic inflammation.

There were several limitations in our study. First, this was a retrospective single-center study. The current findings of our study need to be validated in future large, prospective multicenter study. Second, our study population are limited to hepatitis viral B infection. The results of the current study might not be applied to other liver disease. Finally, our study failed to explore other confounding factors for the diagnostic accuracy of AFP tests in prediction of HCC due to retrospective design.

Conclusion

In conclusion, our study proposed that elevated serum ALT level is strongly associated with abnormal elevated AFP level in patients with hepatitis B without developing HCC. The diagnostic value of AFP tests might be increased by adjusting for serum ALT values with better predictive value in patients with ALT level \leq 2ULN and impaired predictive performance in patients with ALT level > 2ULN. AFP/(ALT \times AST) ratio had a better diagnostic performance than AFP in patients with elevated ALT level.

Abbreviations

HCC, hepatocellular carcinoma; ALT, alanine transaminase; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; AUC, the area under the receiver-operating curve.

Declarations

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Authors' contributions Acquisition of data: Jiahao Chen, Huiqing Zhu, Zhihuan Liu

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Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

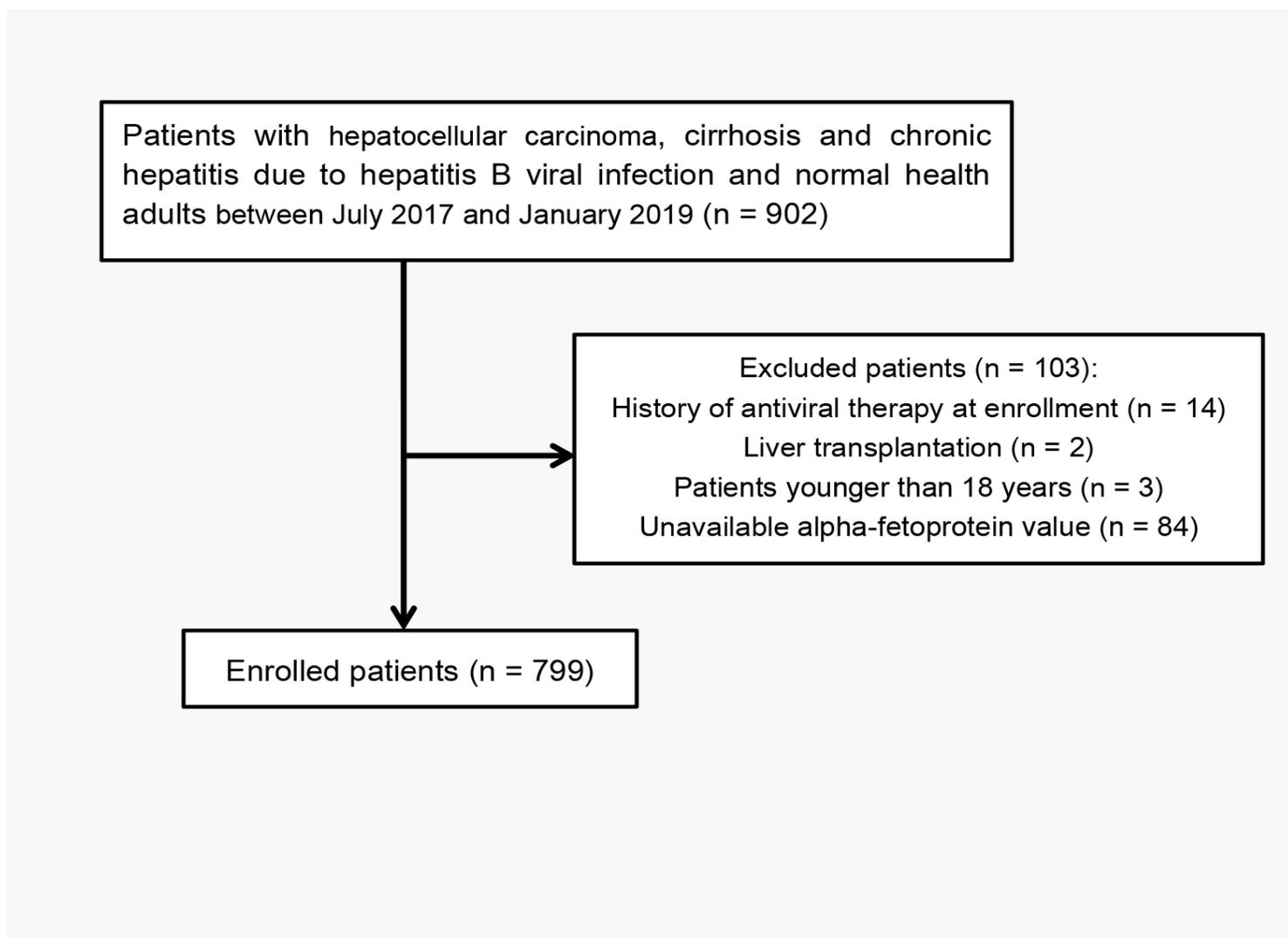
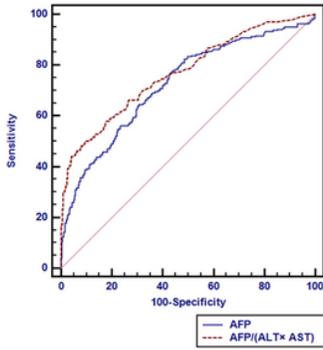
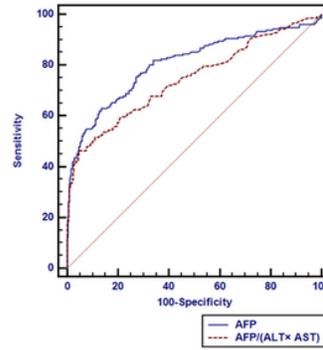


Figure 1

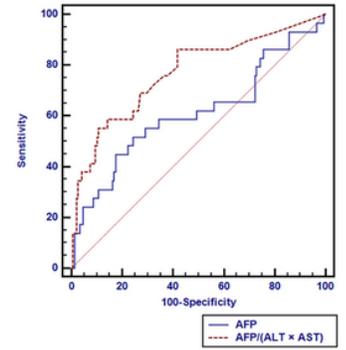
Flow chart of the study population



A



B



C

Figure 2

The area under the receiver-operating curves (AUCs) of alpha-fetoprotein (AFP) and AFP/[alanine transaminase (ALT)×Aspartate aminotransferase (AST)] ratio for detecting hepatocellular carcinoma in total cohort (A), patients with (ALT) level ≤ 2 upper limit of normal (ULN) (B) and patients with ALT level > 2 ULN (C).