Albumin Platelet Product: A Novel Score for Liver Fibrosis Stage and Prognosis.

Koji Fujita (92m7v9@med.kagawa-u.ac.jp)
Kagawa University
Kazumi Yamasaki
Nagasaki Medical Center
Asahiro Morishita
Kagawa University
Tingting Shi
Kagawa University
Joji Tani
Kagawa University
Noriko Nishiyama
Kagawa University
Hideki Kobara
Kagawa University
Takashi Himoto
Kagawa Prefectural College of Health Sciences
Hiroshi Yatsuhashi
Nagasaki Medical Center
Tsutomu Masaki
Kagawa University

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Abstract

Fibrosis-4 index, a conventional biomarker for liver fibrosis stage, is confounded by age and hepatitis activity grade . The current retrospective multicenter study aimed to formulate the novel indices of liver fibrosis by mathematically combining items of peripheral blood examination and to evaluate ability of prognosis prediction. After a novel index was established in a training cohort, the index was tested in a validation cohort. Briefly, a total of 426 patients were enrolled in a training cohort. Albumin and platelet most strongly correlated to fibrosis stage among blood examination. Albumin platelet product (APP) = Albumin × platelet / 1000 could differentiate the four stages of liver fibrosis ($p < 0.05$). APP indicated fibrosis stage independent from hepatitis activity grade. A cut-off value = 4.349 diagnosed cirrhosis with area under ROC more than 0.8. Multivariate analysis revealed that smaller APP independently contributed to HCC prevalence and overall mortality. The results were validated in another 707 patients with HCV infection. In conclusion, APP was not confounded by age or hepatitis activity grade contrary to Fibrosis-4 index. APP is as simple as physicians can calculate it by pen calculation. The product serves physicians in managing patients with chronic liver disease.

Introduction

Liver disease brings the world approximately 2 million of annual deaths [1]. One half of the liver disease-related deaths attributes to cirrhosis, the most progressed status of liver fibrosis. Evaluation of liver fibrosis stage enables a physician to predict and prevent patients from several complications of cirrhosis including esophagogastric varix, ascites, and hepatic encephalopathy expected in the future [2]. Hepatocellular carcinoma (HCC), the sixth leading malignancy and the third common cause of cancer death [3], also typically complicates patients with cirrhosis [4].

Liver biopsy examination used to be the gold standard for staging liver fibrosis.

However, noninvasive strategies to estimate fibrosis stage have already been replacing it [5]. The most inexpensive and simple modality should be several indices combining some items from complete blood count and liver function test, as represented by Fibrosis-4 index (FIB-4) [6,7].

However, FIB-4 index has been reported to be confounded by age and hepatitis activity grade [8,9]. Furthermore, the index is difficult to calculate without ready-made online calculators. In the current retrospective multicenter study, we formulated a novel index of the liver fibrosis stage and prognosis by mathematically combining two items of peripheral blood examination in a training cohort, and validated their clinical significance in a validation cohort.

Methods

Study design

The current retrospective study investigated novel indices for liver fibrosis and prognosis consisting of two or three blood exams. Clinical information and pathological stage of liver fibrosis were available to readers of the novel index, but not available to the liver pathologists.

After a novel index was established in a training cohort, the index was tested in a validation cohort. Diagnostic potential for liver fibrosis stage was described by area under ROC curve, sensitivity, specificity and positive

likelihood ratio. Prognosis prediction by a novel index was presented using two endpoints, prevalence of HCC and overall deaths. Multivariate analysis was performed to process potential confounders within allowable number of parameters ruled by number of events [10]. To control any potential biases in a training cohort, clinical significance of a novel index was evaluated in a validation cohort. Sample size was validated based on post-hoc power analysis. The study was performed according to STARD and STROBE statement [13,14].

Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Kagawa University, Faculty of Medicine (Heisei-30-151) [15]. Informed consent was obtained from all subjects or, if subjects are under 18, from a parent and/or legal guardian

Generation of novel fibrosis indices

To select candidate blood exam items for a novel index, linear trend through fibrosis stage was evaluated for them. Considering R squares, two or three items were mathematically combined as a simple product or ratio.

A training cohort

Japanese patients with HCV and HBV infection, primary biliary cirrhosis definite and probable autoimmune hepatitis patients who underwent percutaneous liver biopsy examinations for a clinical condition between 1986 and 2019 in Kagawa University Hospital, were consecutively enrolled. Patients who had hepatocellular carcinoma when the liver biopsy examinations were performed were excluded.

Clinical data

The following clinical data were extracted from the participants' medical records: age, gender, platelet count, AST, ALT, γGTP, T-Bil, total protein and albumin in blood examinations. T-Bil (mg/dl) was converted to T-Bil (μmol/l) according to the equation: T-Bil (mg/dl) × 17.1. FIB-4, a conventional liver fibrosis index, was calculated using the following equation: age × AST (U/l) / (Plt (10^9/l) × √ALT (U/l)) [16]. APRI was calculated using the following equation: 100 × (AST (U/l) / upper limit of normal AST values (U/l)) / (Plt (10^9/l) [17]. GPR was calculated using the following equation: 100 × (γGTP (U/l) / upper limit of normal γGTP values (U/l)) / (Plt (10^9/l) [18]. ALBI score was calculated according to its original report: Log 10 T-Bil (μmol/l) × 0.66 + Alb (g/l) × (-0.085) [19].

HCV infection was confirmed by polymerase chain reaction, combined reverse transcription-PCR, or branched chain DNA probe assay. For IFN therapy, nonpegylated IFNs, including natural IFN alpha and beta and recombinant IFN alpha-2a, alpha-2b and beta, were employed. Pegylated IFNs were also administered with or without ribavirin. Direct antiviral agents including telaprevir, simeprevir, asnaprevir, daclatasvir, sofosbuvir were also applied. Sustained viral response (SVR) was defined as negative HCV RNA in sera 6 months or later after IFN therapy was completed. Patients who failed to achieve SVR were regarded no viral response (non SVR).

HBV infection was determined by positive HBsAg, HBeAg, HBeAb, HBcAb, or DNA polymerase described in medical records.

Serological diagnosis of PBC was performed using an anti-mitochondrial antibody and an anti-mitochondrial M2 antibody [20]. Data for the anti-centromere antibody was also extracted for patients who were followed up for one

year or more [21].

Definite and probable AIH was diagnosed according to IAIHG criteria revised in 1999 [22].

Histopathological analysis

For HCV, HBV, and AIH samples of liver biopsies, the extent of fibrosis was assessed using a modified METAVIR score (modified from [23]) as follows: stage 1, portal or central fibrosis; stage 2, some septa; stage 3, many septa; stage 4, cirrhosis. The METAVIR grading system was used to assess hepatic inflammatory activity [24]. Pathological stage of PBC was evaluated using the Scheuer classification (stage 1, florid duct lesion; stage 2, ductular proliferation; stage 3, scarring; and stage 4, cirrhosis) by experienced pathologists who specialized in liver pathology [25,26]. Staging and grading were performed by experienced pathologists who specialized in liver pathology.

A validation cohort

A validation cohort was identical from patients in a past report investigated for WFA^{+}-M2BP, a serum biomarker of liver fibrosis [11]. As shown in the past report, the validation cohort comprised 707 patients with HCV infection, including 274 patients with fibrosis stage 0-1; 193 with stage 2; 120 with stage 3; and 120 patients with stage 4. All other clinical data of the validation cohort were identical to those in the past report.

Statistical analysis

Continuous variables were presented as median and interquartile ranges. Mann-Whitney *U* test was used for comparison between average and median values. Kruskal-Wallis' analysis of variance (ANOVA), followed by the Steel-Dwass *post hoc* test, was used to assess significant differences in terms of fibrosis stages (F0-1, F2, F3, and F4). Categorical variables were analyzed using Fisher's exact test. Cut-off values in ROC analysis were determined using Youden index [27]. $P < 0.05$ was considered statistically significant.

For the training cohort, statistical analyses above were performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) [28,29], at Kagawa University.

For the validation cohort, the abovementioned statistical analyses were performed using SPSS statistical software version 26.0 (SPSS, Inc., Chicago, IL), JMP 14 (SAS Institute Inc., Cary, NC), and EZR at Nagasaki Medical Center.

Results

Characteristics of the training cohort

According to diagram in Figure 1, a total of 426 patients comprising 252 of HCV patients, 27 of HBV patients, 52 of PBC patients, and 95 of AIH patients were enrolled in this study (Table 1). Based on the liver biopsy examinations, 128 patients had pointed out stage 1 fibrosis; 149 had stage 2 fibrosis; 114 had stage 3 fibrosis and 35 had stage 4 fibrosis. Among them, 336 patients were followed up for 1 year or more. The longest follow up period was 32 years. Hepatocellular carcinoma (HCC) was pointed out in 45 patients and 42 ones died.

Generation of Albumin platelet product

To determine items of an equation, linear trend through fibrosis staging was evaluated for age, platelet, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), and gamma-glutamyl transpeptidase (γGTP). Among them, age and T-Bil linearly increased, and platelet and albumin decreased (Table 1). R squares were greater than 0.1 in platelet and Alb. Age and T-Bil had lower R squares than 0.1. Combining T-Bil, platelet and albumin mathematically, four equations were generated; Alb × Plt / 1000, Albumin platelet product (APP) ; Alb / T-Bil, Albumin bilirubin quotient; 10 × T-Bil / platelet, Bilirubin platelet quotient; Alb × Plt / (T-Bil × 100), Three math.

Diagnostic ability of novel indices for liver fibrosis staging in the training cohort

Differences in median values between two fibrosis stages were analyzed for four indices using Steel-Dwass test (Figure 2). The results showed that the APP could differentiate any four stages (**a**). The albumin bilirubin quotient (**b**), bilirubin platelet quotient (**c**), and three math Alb × Plt / (T-Bil × 100) (**d**), could differentiate fibrosis stage 3 from stage 2 and stage 4 from stage 3, whereas they failed to differentiate between stage 1 and 2.

Receiver operating characteristic (ROC) analysis was performed to assess the ability to distinguish advanced fibrosis (F3-4) from nonadvanced fibrosis (F0-2) and cirrhosis (F4) from noncirrhotic stages (F0-3). As shown in Figure 3, area under ROC (AUROC) of four indices to distinguish advanced fibrosis from nonadvanced fibrosis was greater than 0.7 (**a-d**). A cut-off value of APP to differentiate F3-4 from F0-2 was determined at 6.395 with 0.7383 of sensitivity, 0.7220 of specificity, and 2.656 of positive likelihood ratio (**a**).

The AUROC of the indices to detect cirrhosis differentially from noncirrhotic stages resulted greater than 0.8 in APP (**a**), Bilirubin platelet quotient (**c**) and Three math (**d**) as shown in Figure 4. The AUROC of Albumin bilirubin quotient stayed smaller than the others (**b**). A cut-off value of APP to differentiate F4 from F0-1 was determined at 4.349 with 0.7143 of sensitivity, 0.8670 of specificity, and 5.371 of positive likelihood ratio.

The greatest AUROC was presented by APP among four indices. The second was Three math. Based on the analyses above, APP and Three math were extracted as candidates of liver fibrosis staging.

Comparison between APP and conventional indices in the training cohort

Differences in median values between two fibrosis stages were analyzed for FIB-4 (**a**), AST to platelet ratio index (APRI, **b**), γGTP to platelet ratio index (GPR, **c**) and Albumin bilirubin score (ALBI score, **d**) using the Steel-Dwass test (Figure 5). As a result, FIB-4 and ALBI score differentiated fibrosis stage 3 from stage 2 and stage 4 from stage 3 whereas they failed to differentiate between F0-1 and 2 ($p < 0.05$). APRI did not distinguish stage 4 from stage 3. GRP was not significantly different between F0-1 and 2 and between F3 and 4.

ROC analysis revealed, as shown in Figure 6, that AUROC of FIB-4 (**a**) and ALBI score (**b**) to distinguish advanced fibrosis from nonadvanced fibrosis ranged between 0.7 and 0.8. The AUROCs to detect cirrhosis differentially from noncirrhotic stages were determined between 0.8 and 0.9 (**c**, **d**). Compared to FIB-4 and ALBI score, APP revealed competitive in staging of liver fibrosis based on ROC analyses.

Prognosis prediction by APP in the training cohort

In total, 336 patients were followed up for at least one year in the training cohort. Kaplan-Meyer analysis was performed in the training cohort to estimate the contribution of the APP to HCC-free survival and overall survival. As shown in Figure 7, a cut-off value = 6.395 could significantly differentiate HCC-free survival (**a**) and overall

survival (**b**). Survival rates at 15 year were 91.2 % and 75.9 % for HCC free survival; 95.2 % and 77.7 % for overall survival. Another cut-off value = 4.349 also stratified HCC prevalence (**c**) and mortality (**d**) in the training cohort. Survival rates at 15 year were 87.1 % and 71.5 % for HCC free survival; 93.6 % and 55.6 % for overall survival.

Post-hoc power analysis resulted in a power = 0.975 for HCC-free survival and 0.998 for overall survival using a cut-off value = 6.395. When the training cohort was stratified using an alternative cut-off value = 4.349, HCC-free and overall survival was proved with power 0.808 and 1.000.

A multivariate analysis in a training cohort

To investigate predictive ability of APP, Cox proportional hazard model was applied on follow up data of the training cohort. Concerning four variables, age, gender, etiology and APP, hazard ratios were analyzed to determine whether APP independently contribute to HCC prevalence and mortality in the training cohort. As shown in Table 2, both of APP < 6.395 and 4.349 significantly increased HCC prevalence and mortality. The proportional hazard model analysis was validated with 4 variables for 45 patients with HCC or 42 deaths (Table 1) [10].

Characteristics of HCV-specific subpopulation in the training cohort

To probe diagnostic accuracy of liver fibrosis and contribution to prognosis prediction by APP further, a cohort with HCV infection was extracted from the training cohort. As shown in Table 3, 252 patients presented a distribution of liver fibrosis stage as follows; 58 of stage 1, 93 of stage 2, 72 of stage 3 and 29 of stage 4. Similar to results in the training cohort, Total bilirubin increased along with fibrosis progression while platelet and albumin decreased.

Among the sub-cohort with HCV infection, 191 patients were followed up for the median 10 years. The longest follow up period recorded 29 years. Sustained viral response was confirmed 86 patients after antiviral therapy subsequent to baseline liver biopsy examination. Thirty-seven patients were complicated with HCC and 25 ones were described died.

Diagnostic ability of liver fibrosis staging in HCV-specific subpopulation in the training cohort

Differences in median values between two fibrosis stages were evaluated for APP (**a**) and FIB-4 (**b**), as shown in Figure 8. Both of the indices differentiated fibrosis stage 3 from stage 2 and stage 4 from stage 3 (p<0.05).

ROC analysis revealed that AUROC of APP to distinguish advanced fibrosis from nonadvanced fibrosis was greater than 0.8 (**a**), as shown in Figure 9. Youden index determined a cut-off value of 6.395, which is identical to the cut-off value in the training cohort. Cirrhosis was also divided from noncirrhotic status with AUROC > 0.8 by APP (**b**). A cut-off value = 4.349 was also identical to the value in the training cohort.

The AUROCs of APP were greater than that of FIB-4 in both case of F0-2 versus F3-4 (**c**) and F0-3 versus F4 (**d**). Diagnostic accuracy of APP was also clarified in HCV-specific population.

Influence of Hepatitis Activity on Fibrosis indices

Indices of liver fibrosis have been reported to fluctuate according to hepatitis activity grading [9]. In 93 patients with stage 2, APP in grade 0-1 patients did not differ from that in grade 2 patients (Figure 8**c**). In case of 72 patients

with stage 3, APP was not significantly different between grade 1-2 and 3 patients (**d**). However, FIB-4 was significantly fluctuated in stage 2 and 3 patients (**e, f**).

Prognosis prediction by APP in HCV-specific subpopulation in the training cohort

To determine prognostic value of APP in HCV-specific subpopulation, Kaplan Meier curve was calculated using follow up data of 191 of HCV patients. As a result, APP < 6.395 at baseline meant poorer HCC-free survival compared to those with APP ≥ 6.395, while overall survival was not differentiated by the cut-off value = 6.395 (Figure 10**a**, **b**). Survival rate at 15 year was 96.0 % and 67.2 % for HCC free survival. APP < 4.349 predicted significantly poorer HCC-free survivals and overall survival (**c**, **d**). Survival rate at 15 year was 83.3 % and 62.0 % for HCC free survival and 92.1 % and 59.6 % for overall survival.

Post-hoc power analysis resulted in a power = 0.998 for HCC-free survival using a cut-off value = 6.395. When the training cohort was stratified using an alternative cut-off value = 4.349, HCC-free and overall survival was proved with power 0.819 and 0.998.

A multivariate analysis in HCV-specific subpopulation in the training cohort

Cox proportional hazard model was applied on follow up data of HCV-specific subpopulation in the training cohort. Considering four variables, age, gender, viral response to antiviral therapy and APP, hazard ratios for HCC prevalence and mortality were calculated. As shown in Table 4, APP < 6.395 yielded significant increase of HCC prevalence. APP < 4.349 also increased of both HCC prevalence and mortality.

However, based on the criteria, number of variables exceeded 10 times of events; 37 patients with HCC and 25 deaths, as shown in Table 3 [10]. Thus, a validation study was prepared to clarify clinical significance of APP for HCV-specific cohort.

Diagnostic ability of liver fibrosis staging in the validation cohort

To evaluate the diagnostic ability of liver fibrosis staging, the APP was calculated for each fibrosis stage in the validation cohort. As shown in Figure 11, the APP was able to differentiate the four stages of fibrosis ($p < 0.05$).

ROC analysis revealed that the AUROCs of the APP for distinguishing advanced fibrosis from nonadvanced fibrosis (**a**) and cirrhosis from noncirrhotic status (**b**) were greater than 0.8 (**c**), as shown in Figure 12. The AUROCs of the APP were greater than that of FIB-4 or APRI (**c**). The diagnostic abilities of the APP with two cut-off values are summarized in Table 5. Both cut-off values, APP = 6.395 and = 4.349, were characterized by negative predictive values relatively greater than 80%.

Prognosis prediction by the APP in a validation cohort

The clinical impact of the APP on HCC-free survival and overall survival was confirmed using Kaplan-Myer analysis in the validation cohort through 15 years observation (Figure 13). Patient number of HCC complication and death at 15 year was 143 and 73. Each cut-off value, APP = 6.395 and 4.349, could differentiate HCC-free survival in 707 patients with HCV infection (**a, b**). Overall survival was also stratified by two cut-off values (**c, d**).

Post-hoc power analysis resulted in a power = 1.000 for four comparison above between greater and smaller APP groups.

The Cox proportional hazard model was also applied on the validation cohort using a stepwise method, as shown in Table 6. The performances of interferon therapy, sex, age, serum AFP and WFA^+-M2BP levels were included in the multivariate analyses. The results showed that APP < 6.395 contributed to a greater risk of HCC complication. APP < 4.349 also indicated increased prevalence of HCC and death. Number of variables did not exceed 10 times of HCC patients or death [10,11].

Discussion

The current multicenter study presented that 1) APP is able to diagnose fibrosis stage, especially, advanced liver fibrosis and cirrhosis without confounding by age or hepatitis activity grade. 2) Smaller APP independently correlates with greater HCC prevalence and mortality.

Among conventional indices for liver fibrosis, FIB-4 was more reliable according to ROC analysis than APRI or GPR in the current study. Including age in its equation, FIB-4 is reported to overestimate fibrosis stage in senior patients [12]. Thus, a cut-off value of FIB-4 is proposed for each age group [8]. However, APP is not confounded by age because the index is not based on age.

Fibrosis staging by APP equals in accuracy to FIB-4. Diagnostic ability of APP was lined by stability of it against hepatitis activity grading. We previously reported that FIB-4, APRI, enhanced liver fibrosis score (ELF score) and Wisteria *floribunda* agglutinin-positive Mac-2 binding protein (WFA^+-M2BP) fluctuated in an identical fibrosis stage according to activity grade [9]. APP might be more suitable for fibrosis staging than other indices.

FIB-4 consists of four items, age, AST, platelet, and square root of ALT. Calculating FIB-4 using an electronic calculator is not easy in general practice because the square root of ALT locates as one of Denominators in the equation. Therefore, customized calculators for FIB-4 have been open in the internet. Equations of APRI and GPR are simpler compared to FIB-4. However, diagnostic abilities of APRI and GPR for liver fibrosis were not competitive to that of FIB-4 in the current cohort.

In summary, the data probed that APP was as reliable as FIB-4 in liver fibrosis staging. In addition, the equation of APP is as simple as APRI and GPR because APP is calculated by two items alone. Physicians in office can calculate APP by an electronic calculator or even by pen calculation.

The limitations of the current study might lie in the fact that because the current observation focused on patients with HCV infection patients, eligibility of APP in patients with other etiologies should be evaluated in further studies.

In conclusion, APP indicates liver fibrosis stage and prognosis in Japanese patients with chronic liver diseases. The diagnostic accuracy of APP to differentiate fibrosis stage was competitive to that of FIB-4, and free from confounding by age or hepatitis activity. Furthermore, smaller APP independently contributes to HCC prevalence and mortality. APP enables physicians to manage patients with chronic liver diseases.

Abbreviations

Autoimmune hepatitis, AIH; AST to platelet ratio index, APRI; Enhanced liver fibrosis score, ELF score; Fibrosis-4 index, FIB-4; γGTP to platelet ratio index, GPR; Hepatocellular carcinoma, HCC; Hepatitis B virus, HBV; Hepatitis C

virus, HCV; Primary biliary cholangitis, PBC; Wisteria *floribunda* agglutinin-positive Mac-2 binding protein, WFA^+-M2BP

Declarations

Author contribution: All authors have participated in the preparation of the manuscript. The author's contributions are as follows; study concept and design by KF; acquisition of data by AM, TS, JT, NN and HK; analysis and interpretation of data by KF and KY; drafting of the manuscript by KF; critical revision of the manuscript for important intellectual content by TH and HY; statistical analysis by KF and KY; study supervision by TM. They have read the manuscript and have approved this submission.

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References

1. Mokdad, A. A. *et al.* Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med* **12**, 145 (2014).
2. Starr, S. P. & Raines, D. Cirrhosis: diagnosis, management, and prevention. *Am Fam Physician* **84**, 1353-1359 (2011).
3. Forner, A., Reig, M. & Bruix, J. Hepatocellular carcinoma. *Lancet* **391**, 1301-1314 (2018).
4. Granito, A. & Bolondi, L. Non-transplant therapies for patients with hepatocellular carcinoma and Child-Pugh-Turcotte class B cirrhosis. *Lancet Oncol* **18**, e101-e112 (2017).
5. Tapper, E. B. & Lok, A. S. F. Use of Liver Imaging and Biopsy in Clinical Practice. *N Engl J Med* **377**, 2296-2297 (2017).
6. Guha, I. N. *et al.* Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology* **47**, 455-460 (2008).
7. Vallet-Pichard, A. *et al.* FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology* **46**, 32-36 (2007).
8. McPherson, S. *et al.* Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. *Am J Gastroenterol* **112**, 740-751 (2017).
9. Fujita, K. *et al.* Fibrosis Staging Using Direct Serum Biomarkers is Influenced by Hepatitis Activity Grading in Hepatitis C Virus Infection. *J Clin Med* **7** (2018).
10. Peduzzi, P., Concato, J., Feinstein, A. R. & Holford, T. R. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* **48**, 1503-1510 (1995).
11. Yamasaki, K. *et al.* Elevated serum levels of Wisteria floribunda agglutinin-positive human Mac-2 binding protein predict the development of hepatocellular carcinoma in hepatitis C patients. *Hepatology* **60**, 1563-1570 (2014).
12. Wai, J. W., Fu, C. & Wong, V. W. Confounding factors of non-invasive tests for nonalcoholic fatty liver disease. *J Gastroenterol* **55**, 731-741 (2020).

13. Cohen, J. F. *et al.* STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* **6**, e012799 (2016).
14. von Elm, E. *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* **147**, 573-577 (2007).
15. Association, W. M. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* **310**, 2191-2194 (2013).
16. Sterling, R. K. *et al.* Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* **43**, 1317-1325 (2006).
17. Wai, C. T. *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* **38**, 518-526 (2003).
18. Lemoine, M. *et al.* The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut* **65**, 1369-1376 (2016).
19. Johnson, P. J. *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* **33**, 550-558 (2015).
20. Gershwin, M. E. *et al.* Molecular biology of the 2-oxo-acid dehydrogenase complexes and anti-mitochondrial antibodies. *Prog Liver Dis* **10**, 47-61 (1992).
21. Nakamura, M. *et al.* Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. *Hepatology* **45**, 118-127 (2007).
22. Alvarez, F. *et al.* International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* **31**, 929-938 (1999).
23. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* **20**, 15-20 (1994).
24. Bedossa, P. & Poynard, T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* **24**, 289-293 (1996).
25. Scheuer, P. Primary biliary cirrhosis. *Proc R Soc Med* **60**, 1257-1260 (1967).
26. Scheuer, P. J. Ludwig Symposium on biliary disorders--part II. Pathologic features and evolution of primary biliary cirrhosis and primary sclerosing cholangitis. *Mayo Clin Proc* **73**, 179-183 (1998).
27. YOUDEN, W. J. Index for rating diagnostic tests. *Cancer* **3**, 32-35 (1950).
28. Hens, N., Aerts, M. & Molenberghs, G. Model selection for incomplete and design-based samples. *Stat Med* **25**, 2502-2520 (2006).
29. Kanda, Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* **48**, 452-458 (2013).

Tables

Table 1. Baseline characteristics and follow up information of a training cohort

Fibrosis stage	Total	F0-1	F2	F3	F4	R squared	*P* value
Patient number	426	128	149	114	35	-	-
Age	55	55	54	55	63	0.0169	0.0071
	(44 - 64)	(46 - 64)	(42 - 62)	(44 - 64)	(53 - 67)		
Male / Female	182/244	36/92	74/75	59/55	13/22	-	-
HCV / HBV / PBC / AIH	252/27/52/95	58/8/23/39	93/10/15/31	72/9/12/21	29/0/2/4	-	-
Platelet count (× 10^9/l)	179	215	183	150	106	0.1553	< 0.0001
	(136 - 221)	(174 - 252)	(145 - 226)	(115 - 194)	(74 - 162)		
Total protein (g/l)	74	74	74	74	73	0.0035	0.2285
	(69 - 79)	(70 - 79)	(70 - 80)	(69 - 80)	(67 - 77)		
Albumin (g/l)	38	40	40	37	31	0.1406	< 0.0001
	(34 - 42)	(35 - 42)	(37 - 42)	(34 - 40)	(27 - 37)		
AST (U/l)	59	44	54	82	74	0.0001	0.8335
	(37 - 98)	(29 - 75)	(38 - 96)	(51 - 120)	(50 - 107)		
ALT (U/l)	76	49	76	101	70	0.0029	0.2706
	(41 - 128)	(28 - 113)	(43 - 128)	(66 - 151)	(45 - 104)		
Total bilirubin (μmol/l)	13.8	12.0	12.0	17.2	18.9	0.0503	< 0.0001
	(10.3 - 18.9)	(9.02 - 15.5)	(10.3 - 17.1)	(12.0 - 22.2)	(12.0 - 29.1)		
γGTP (U/l)	58	63	48	67	40	0.0022	0.3406
	(29 - 129)	(26 - 126)	(23 - 107)	(45 - 151)	(22 - 81)		
Followed up cohort							
(at least 1 year)							
patient	336	95	117	100	24	-	-

number							
Follow up period	10	9	11	10	8	-	-
(years)	(5 - 18)	(4 - 18)	(7 - 21)	(5 - 18)	(3 - 10)		
HCC prevalence	45	5	14	16	10	-	-
(patient number, %)	(13.4)	(5.3)	(12.0)	(16.0)	(41.7)		
Death	42	6	18	6	12	-	-
(patient number, %)	(12.5)	(6.3)	(15.4)	(6)	(50)		

AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; PBC, primary biliary cholangitis

Table 2. Prediction of HCC prevalence and mortality by Albumin platelet product in a training cohort

Alb × Plt = 6.395 for HCC complication	HR	95% CI	*P* value
Age	1.059	1.024 - 1.094	0.0008
Male / Female	0.925	0.492 - 1.739	0.8090
Alb × Plt < 6.395 / ≧ 6.395	1.945	1.043 - 3.626	0.0363
AIH / HCV	0.167	0.039- 0.720	0.0165
HBV / HCV	1.968	0.649 - 5.969	0.2316
PBC / HCV	0.088	0.012 - 0.673	0.0191
Alb × Plt = 6.395 for mortality			
Age	1.077	1.035 - 1.120	0.0002
Male / Female	1.007	0.475 - 2.135	0.9857
Alb × Plt < 6.395 / ≧ 6.395	2.020	1.021 - 3.997	0.0434
AIH / HCV	0.501	0.163 - 1.541	0.2282
HBV / HCV	< 0.001	-	0.9965
PBC / HCV	1.708	0.733 - 3.997	0.2148
Alb × Plt = 4.349 for HCC complication			
Age	1.059	1.025 - 1.094	0.0007
Male / Female	1.062	0.559 - 2.020	0.8542
Alb × Plt < 4.349 / ≧ 4.349	2.961	1.503 - 5.834	0.0017
AIH / HCV	0.154	0.036 - 0.664	0.0121
HBV / HCV	2.225	0.746 - 6.639	0.1515
PBC / HCV	0.090	0.012 - 0.678	0.0194
Alb × Plt = 4.349 for mortality			
Age	1.074	1.032 - 1.118	0.0004
Male / Female	1.283	0.604 - 2.723	0.5165
Alb × Plt < 4.349 / ≧ 4.349	4.063	1.984 - 8.324	0.0001
AIH / HCV	0.534	0.175 - 1.626	0.2692
HBV / HCV	< 0.001	-	0.9969
PBC / HCV	1.971	0.870 - 4.467	0.1041

AIH, autoimmune hepatitis; Alb, albumin; Plt, platelet; HBV, hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; PBC, primary biliary cholangitis; 95% CI, 95% confidence interval

Table 3. Baseline characteristics and follow up information of HCV patients in a training cohort

Fibrosis stage	Total	F0-1	F2	F3	F4	R squared	*P* value
Patient number	252	58	93	72	29	-	-
Age	54	52	52	57	63	0.0700	< 0.0001
	(43 - 62)	(38 - 60)	(42 - 60)	(47 - 63)	(55 - 66)		
Male/Female	149/103	29/29	58/35	49/23	13/16	-	-
Platelet count (× 10^9/L)	168	190	179	138	94	0.2610	< 0.0001
	(125 - 202)	(173 - 230)	(139 - 211)	(106 - 174)	(63 - 133)		
Total protein (g/L)	74	73	75	73	74	0.0010	0.5980
	(70 - 78)	(70 - 77)	(71 - 79)	(69 - 77)	(67 - 79)		
Albumin (g/l)	39	41	41	37	34	0.2568	< 0.0001
	(36 - 42)	(39 - 43)	(39 - 43)	(34 - 40)	(28 - 38)		
AST (U/l)	55	36	52	74	76	0.0459	0.0005
	(36 - 86)	(23 - 57)	(35 - 78)	(51 - 103)	(49 - 105)		
ALT (U/l)	77	4	76	101	70	0.0009	0.6200
	(42 - 127)	(25 - 93)	(42 - 128)	(71 - 146)	(41 - 100)		
Total bilirubin (µmol/L)	13.7	12	12.0	17.1	18.8	0.1341	< 0.0001
	(10.3 - 18.8)	(8.6 - 15.4)	(10.3 - 15.5)	(12.0 - 20.5)	(12.8 - 29.1)		
γGTP (U/l)	44	31	38	65	40	0.0130	0.0660
	(24 - 86)	(19 - 67)	(22 - 79)	(39 - 119)	(22 - 77)		
Activity grade (0-1/2/3)	(129/74/20)	(50/7/1)	(64/29/0)	(15/38/19)	-	-	-
Followed up cohort							
(at least 1 year)							
Patient number	191	36	70	65	20	-	-
Follow up period	10	10	11	10	8	-	-
(years)	(6 - 17)	(7 - 18)	(7 - 21)	(5 - 16)	(5 - 10)		
non SVR / SVR	105/86	17/19	36/34	34/31	18/2	-	-
HCC prevalence	37	3	12	12	10	-	-

(patient number, %)	(19.5)	(8.3)	(17.1)	(18.5)	(50.0)		
Death	25	1	12	3	9	-	-
(patient number, %)	(13.1)	(2.8)	(17.1)	(4.6)	(45)		

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; SVR, sustained viral response

Table 4. Prediction of HCC prevalence and mortality of HCV patients in a training cohort

Alb × Plt = 6.395 for HCC complication	HR	95% CI	*P* value
Age	1.054	1.015- 1.095	0.0069
Male / Female	1.016	0.509 - 2.029	0.9638
Alb × Plt < 6.395 / ≧ 6.395	2.216	1.078 - 4.554	0.0304
non SVR / SVR	10.79	2.579 - 45.11	0.0011
Alb × Plt = 6.395 for mortality			
Age	1.112	1.052 - 1.175	0.0002
Male / Female	0.868	0.364 - 2.066	0.7485
Alb × Plt < 6.395 / ≧ 6.395	1.352	0.568 - 3.216	0.4954
non SVR / SVR	1.857	0.675 - 5.110	0.2305
Alb × Plt = 4.349 for HCC complication			
Age	1.060	1.020 - 1.100	0.0026
Male / Female	1.476	0.660 - 3.302	0.3435
Alb × Plt < 4.349 / ≧ 4.349	3.555	1.576 - 8.017	0.0022
non SVR / SVR	11.30	2.678 - 47.68	0.0010
Alb × Plt = 4.349 for mortality			
Age	1.105	1.046 - 1.168	0.0004
Male / Female	1.330	0.482 - 3.671	0.5821
Alb × Plt < 4.349 / ≧ 4.349	3.393	1.256 - 9.165	0.0159
non SVR / SVR	1.865	0.665 - 5.228	0.2361

Alb, albumin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; Plt, platelet; SVR, sustained viral response; 95% CI, 95% confidence interval

Table 5. Diagnostic abilities of Albumin platelet product for liver fibrosis in a validation cohort

Alb × Plt = 6.395		
Stage	F0-2 (n=467)	F3-4 (n=240)
≥ 6.395 (n)	319	148
< 6.395 (n)	53	187
Sensitivity(%)	77.9 (72.1 – 83.0)	
Specificity(%)	68.3 (63.9 – 72.5)	
Positive likelihood ratio	2.46 (2.12 – 2.85)	
PPV(%)	55.8 (50.3 – 61.2)	
NPV(%)	85.8 (81.8 – 89.1)	
Alb × Plt = 4.349		
Stage	F0-3 (n=587)	F4 (n=120)
≥ 4.349 (n)	536	57
< 4.349 (n)	51	63
Sensitivity (%)	52.5 (43.2 – 61.7)	
Specificity (%)	91.3 (88.7 – 93.5)	
Positive likelihood ratio	6.04 (4.42 – 8.26)	
PPV(%)	55.3 (45.7 – 64.6)	
NPV(%)	90.4 (87.7 – 92.6)	

PPV, positive predictive value; NPV, negative predictive value

Table 6. Prediction of HCC prevalence and mortality by Albumin platelet product in a validation cohort

Alb × Plt = 6.395 for HCC complication		Hazard ratio (95% CI)	*P* value
Alb × Plt	< 6.395 / ≧ 6.395	1.87 (1.25 – 2.79)	0.002
IFN therapy	Non-SVR / None	0.72 (0.50 – 1.02)	0.063
	SVR / None	0.13 (0.05 – 0.29)	<0.001
Sex	Male / female	2.11 (1.50 – 2.97)	<0.001
Age	≧57 / < 57	1.90 (1.28 – 2.83)	0.001
AFP	≧7 / < 7 ng/ mL	2.10 (1.38 – 3.18)	0.001
WFA^+-M2BP	≧2.86 / < 2.86	2.22 (1.51 – 3.27)	<0.001
Alb × Plt = 6.395 for mortality			
Alb × Plt	< 6.395 / ≧ 6.395	1.68 (0.95 – 2.98)	0.076
IFN therapy	Non-SVR / None	0.55 (0.34 – 0.91)	0.021
	SVR / None	0.18 (0.06 – 0.51)	0.001
Sex	Male / female	1.74 (1.09 – 2.79)	0.021
Age	≧57 / < 57	2.93 (1.56 – 5.50)	0.001
AFP	≧7 / < 7 ng/ mL	1.77 (0.98 – 3.21)	0.058
WFA^+-M2BP	≧2.86 / < 2.86	2.75 (1.42 – 4.23)	0.001
Alb × Plt = 4.349 for HCC complication			
Alb × Plt	< 4.349 / ≧ 4.349	1.64 (1.10 – 2.45)	0.015
IFN therapy	Non-SVR / None	0.75 (0.52 – 1.07)	0.114
	SVR / None	0.13 (0.06 – 0.31)	<0.001
Sex	Male / female	2.12 (1.51 – 2.99)	<0.001
Age	≧57 / < 57	2.06 (1.39 – 3.06)	<0.001
AFP	≧7 / < 7 ng/ mL	2.31 (1.53 – 3.50)	<0.001
WFA^+-M2BP	≧2.86 / < 2.86	2.20 (1.48 – 3.27)	<0.001
Alb × Plt = 4.349 for mortality			
Alb × Plt	< 4.349 / ≧ 4.349	1.81 (1.06 – 3.11)	0.030
IFN therapy	Non-SVR / None	0.58 (0.35 – 0.97)	0.037
	SVR / None	0.19 (0.07 – 0.54)	0.002
Sex	Male / female	1.77 (1.10 – 2.84)	0.018
Age	≧57 / < 57	3.14 (1.67 – 5.88)	< 0.001
AFP	≧7 / < 7 ng/ mL	1.89 (1.05 – 3.40)	0.035

WFA$^+$-M2BP	≧2.86 / < 2.86	2.29 (1.30 – 4.02)	0.004

HCC, hepatocellular carcinoma; IFN, interferon; SVR, sustained viral response; 95% CI, 95% confidence interval; WFA$^+$-M2BP, Wisteria *floribunda* agglutinin-positive Mac-2 binding protein

Figures

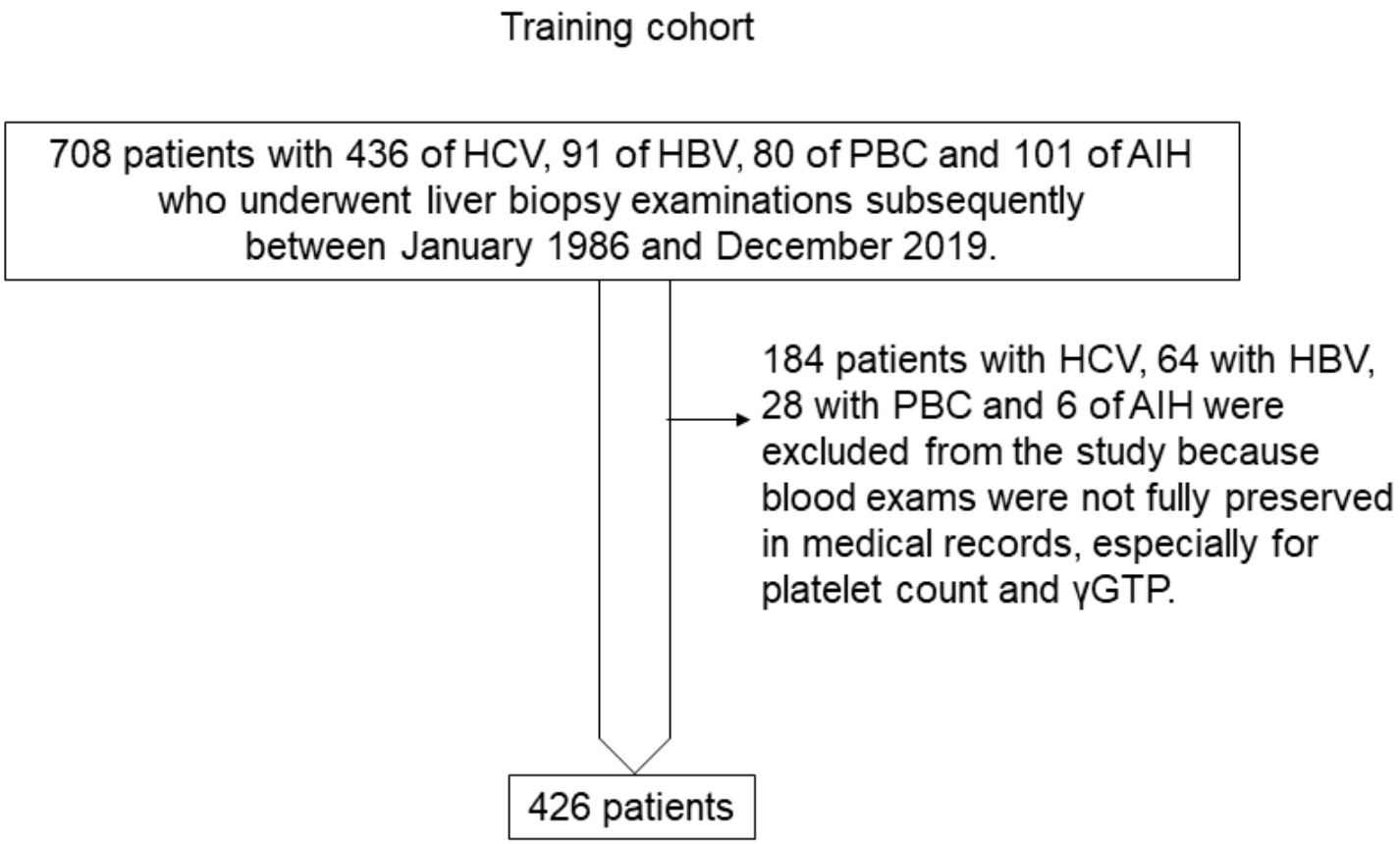
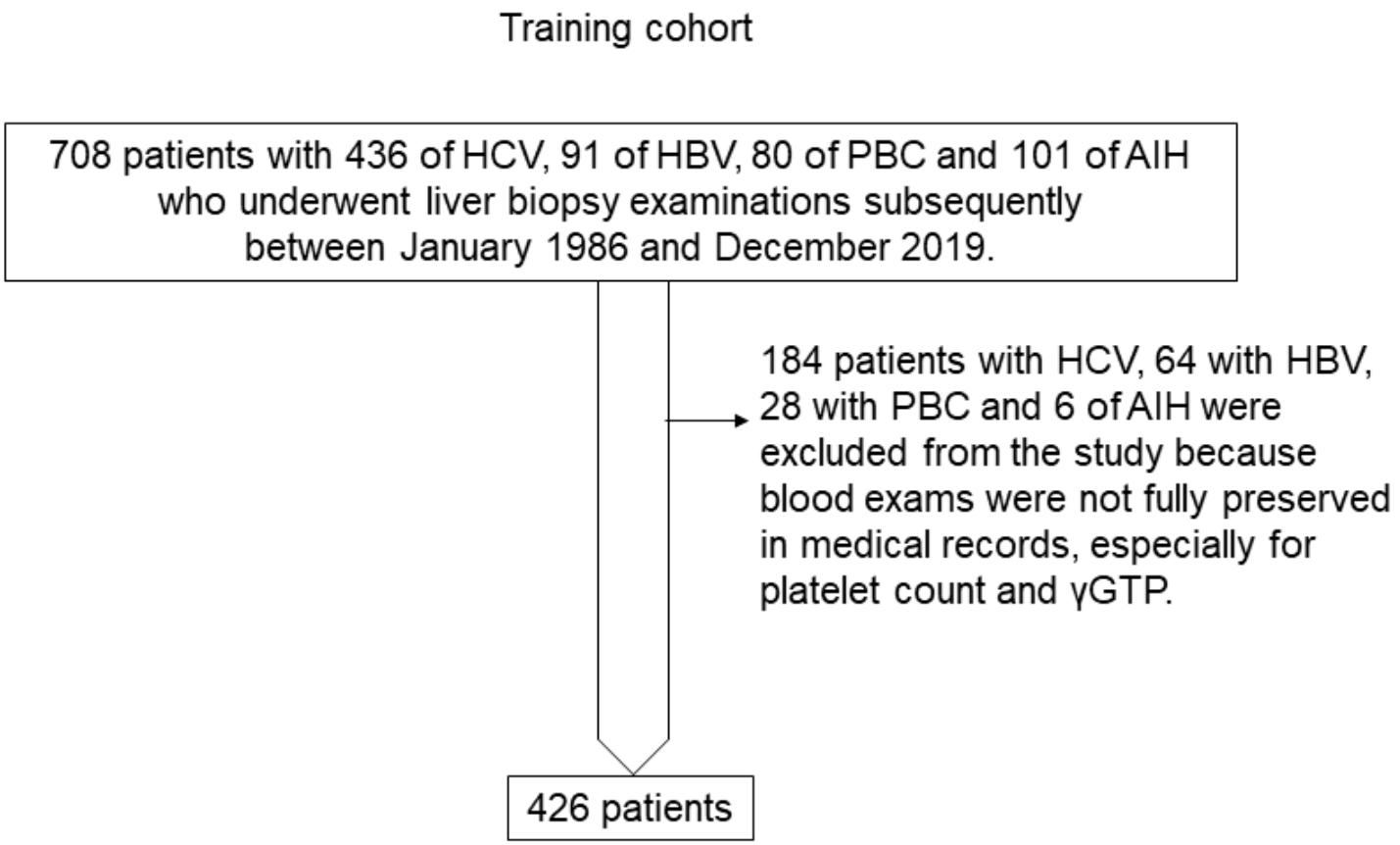


Figure 1

Diagram of training cohort



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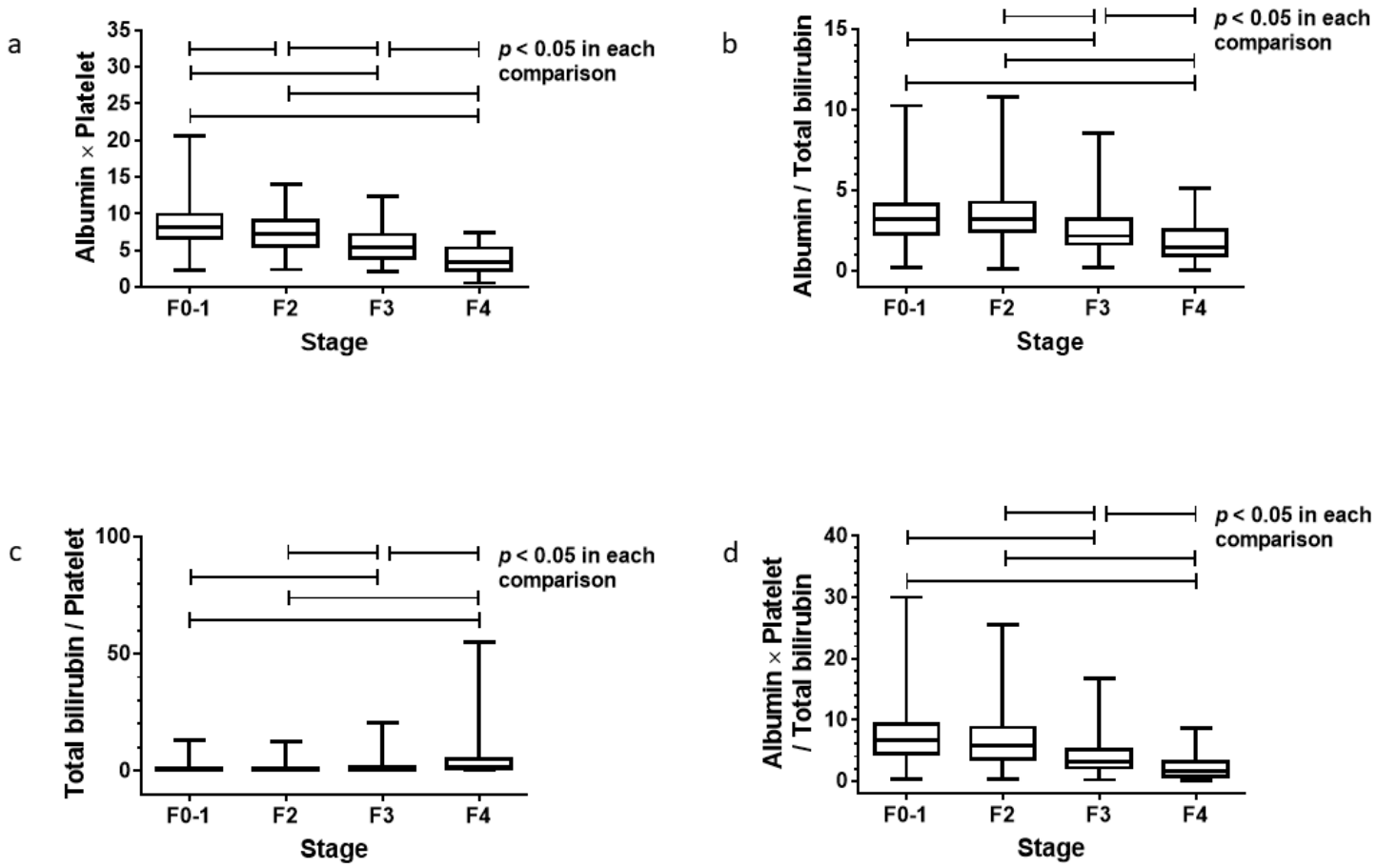
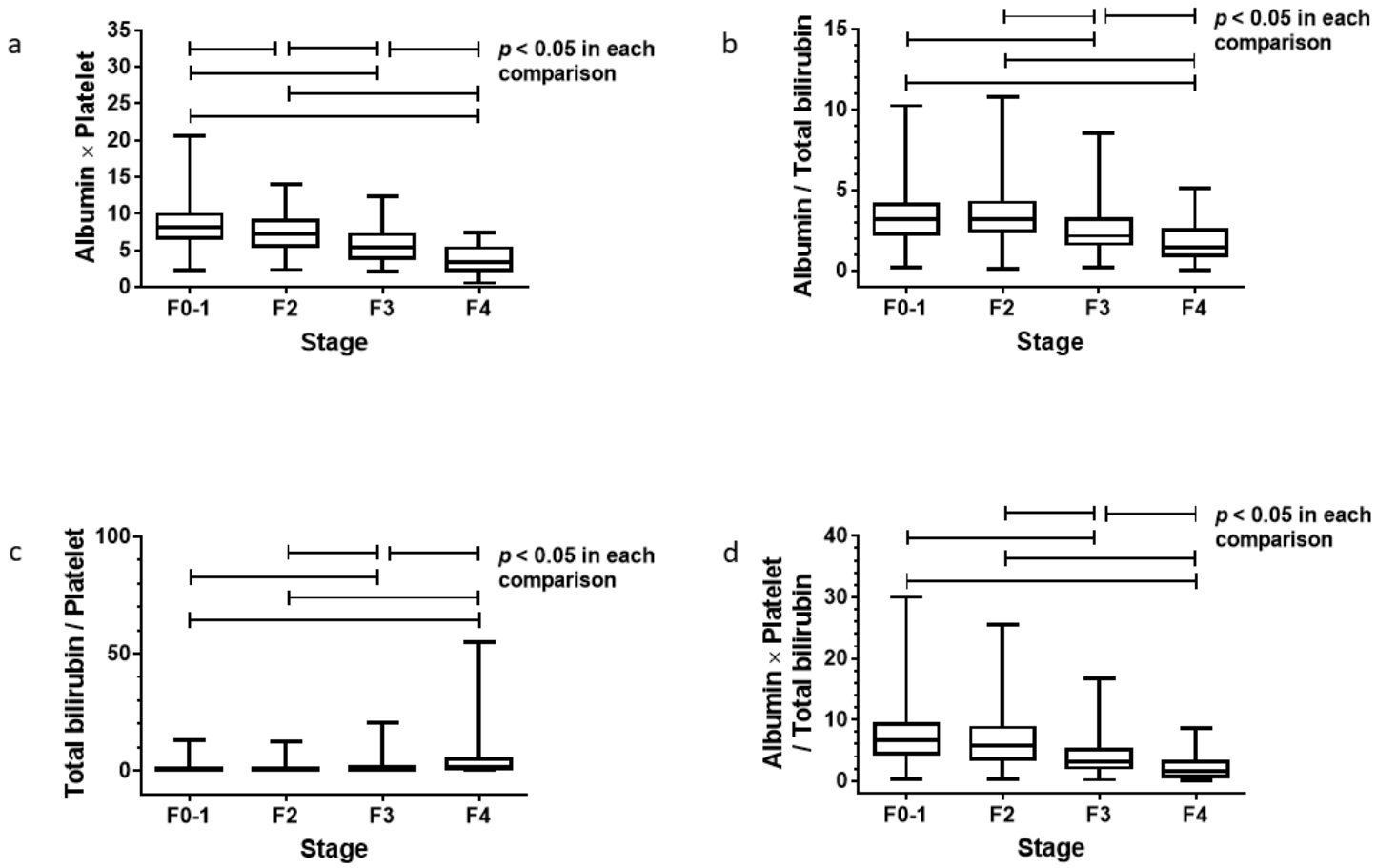


Figure 2

Newly generated fibrosis indices in each fibrosis stage in a training cohort Median values of Albumin platelet product could differentiate each fibrosis stage (a). The other indices, Albumin bilirubin quotient (b), Bilirubin platelet quotient (c) and Three math; Albumin × platelet / (total bilirubin × 100) (d) distinguished stage 4 from stage 3 and stage 3 from stage 2, but failed to differentiate between stage 0-1 and 2 ($p < 0.05$). Data were analyzed using the Steel-Dwass test.



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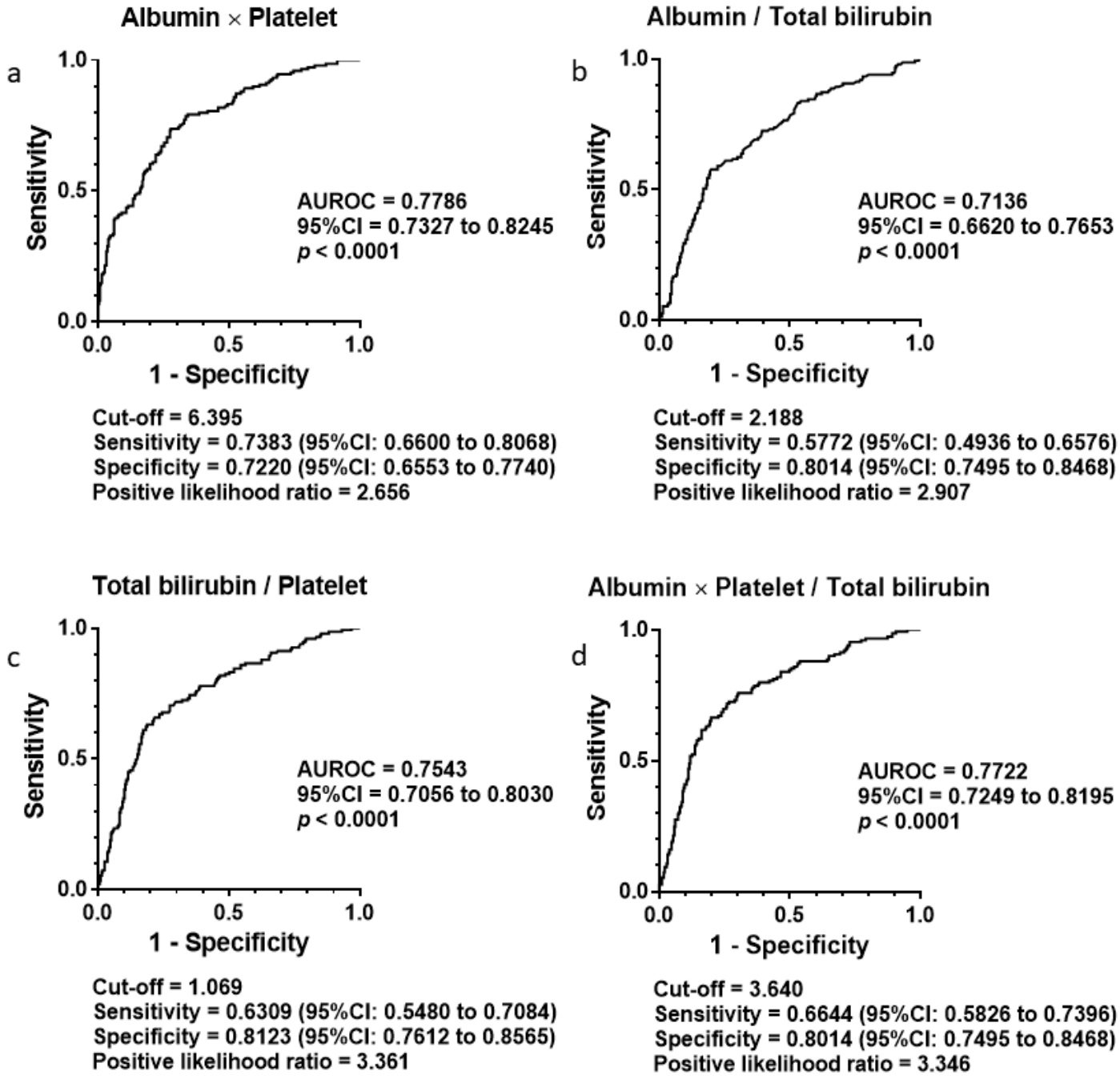
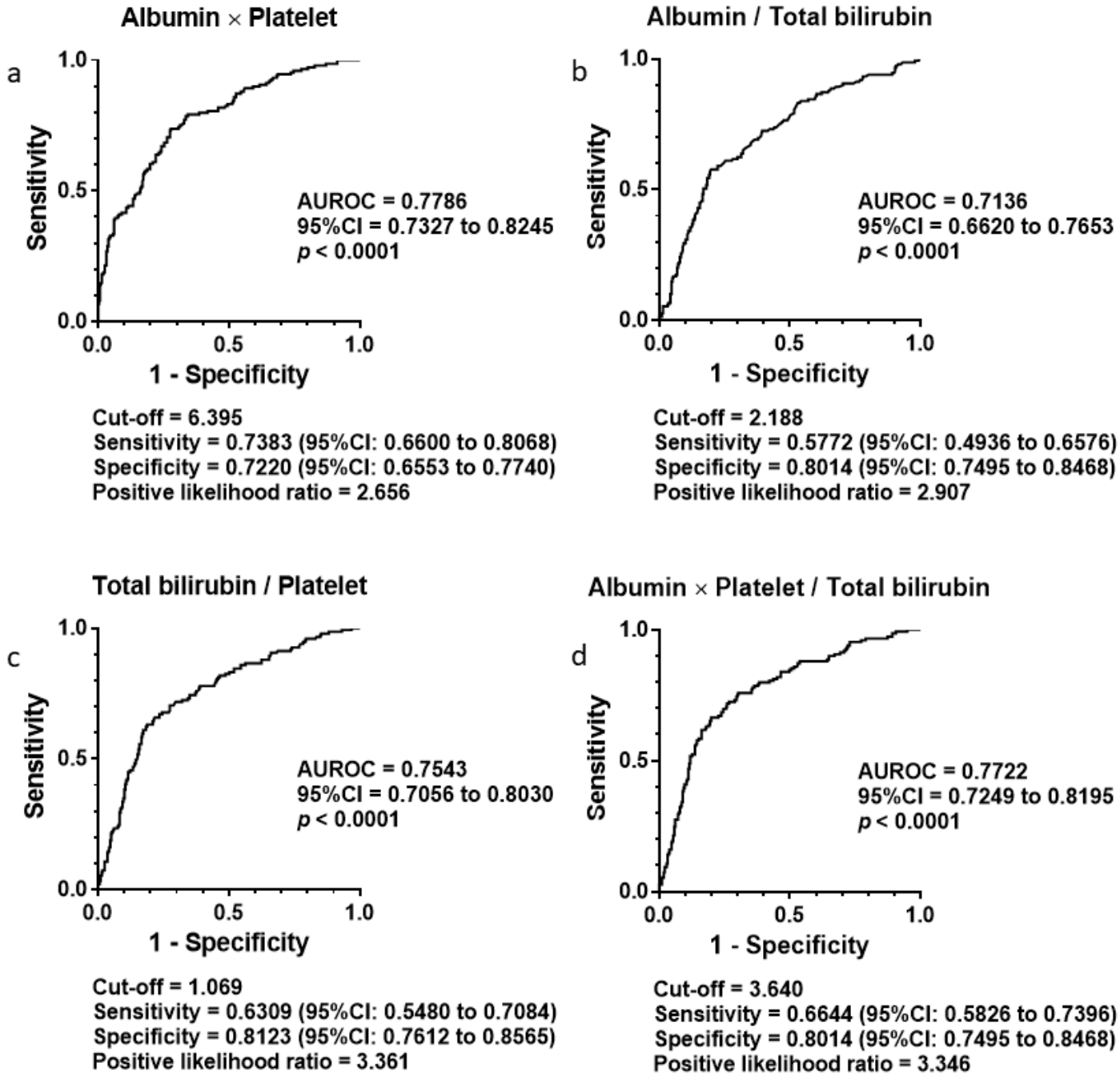


Figure 3

Differential diagnosis of advanced liver fibrosis by newly generated fibrosis indexes in the training cohort ROC analysis to assess the ability of fibrosis indexes to differentiate advanced liver fibrosis (F3-4) from nonadvanced fibrosis (F1-2) yielded AUROC 0.7786 in Albumin platelet product (a), 0.7136 in Albumin bilirubin quotient (b), 0.7543 in Bilirubin platelet quotient (c) and 0.7722 in Three math; Albumin × platelet / (total bilirubin × 100) (d). A cut-off value of Albumin platelet product = 0.6395 presented 0.7383 of sensitivity and 0.7220 of specificity with 2.65 of positive likelihood ratio to differentiate advanced fibrosis from non advanced fibrosis (a). P values less than 0.05 were considered statistically significant.



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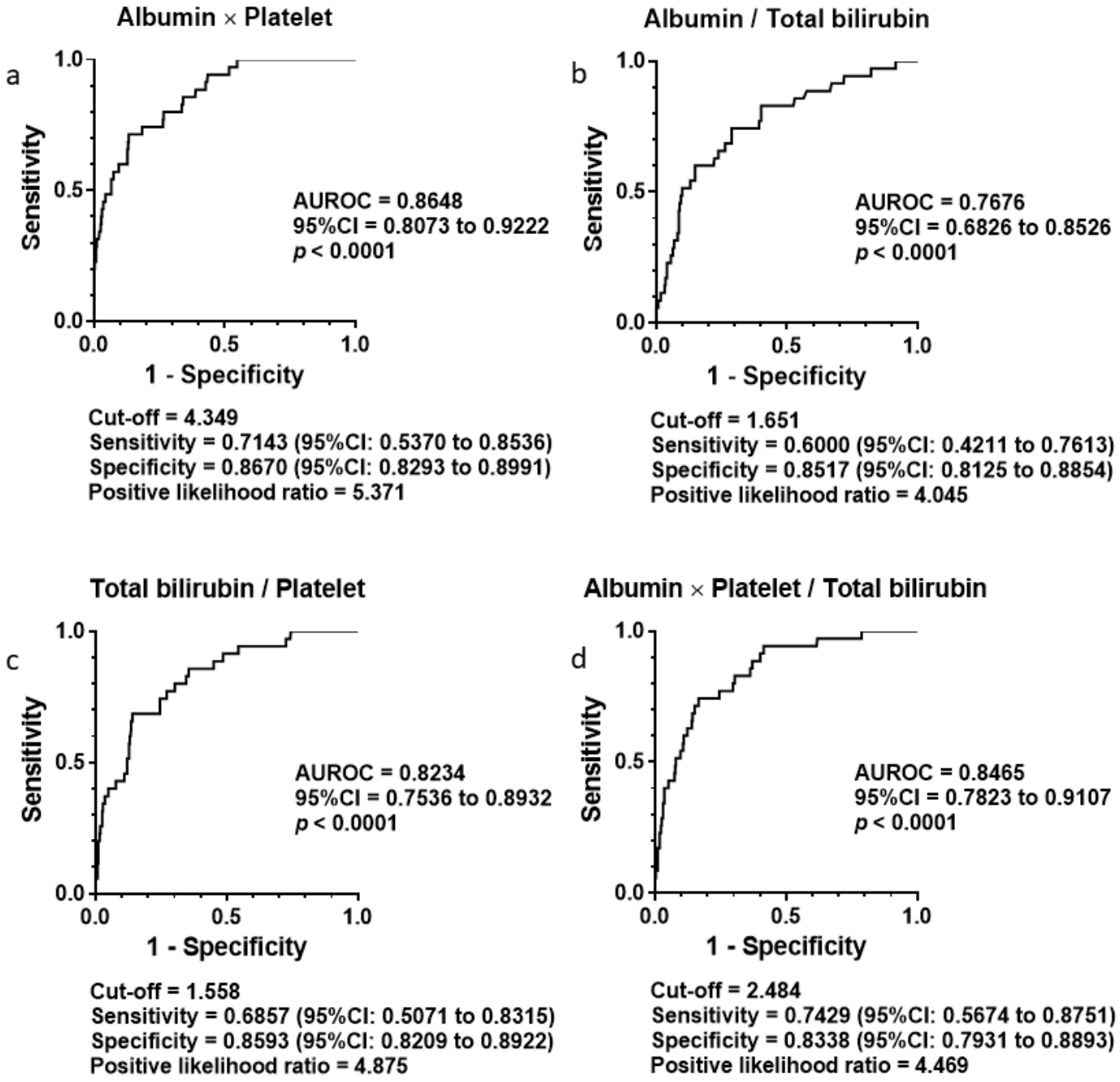
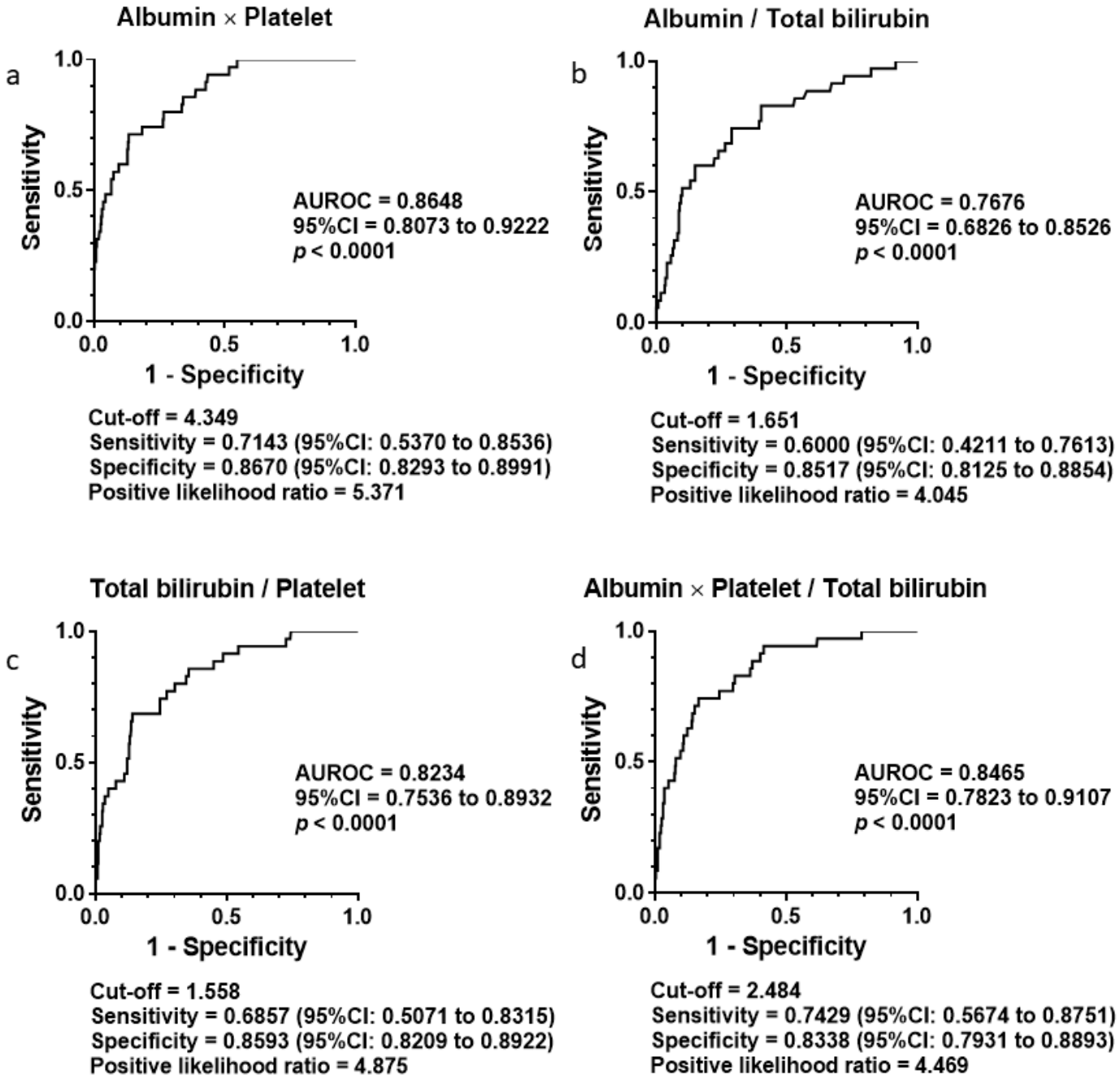


Figure 4

Differential diagnosis of liver cirrhosis by newly generated fibrosis indexes in the training cohort ROC analysis revealed cirrhosis was differentially diagnosed from noncirrhotic status by Albumin platelet product (a), Albumin bilirubin quotient (b), Bilirubin platelet quotient (c) and Three math; Albumin × platelet / (total bilirubin × 100) (d). The greatest AUROC was presented by Albumin platelet product among them. Albumin platelet product = 4.349 determined by Youden Index presented 0.7143 of sensitivity and 0.8670 of specificity with 5.371 (a). P values less than 0.05 were considered statistically significant.



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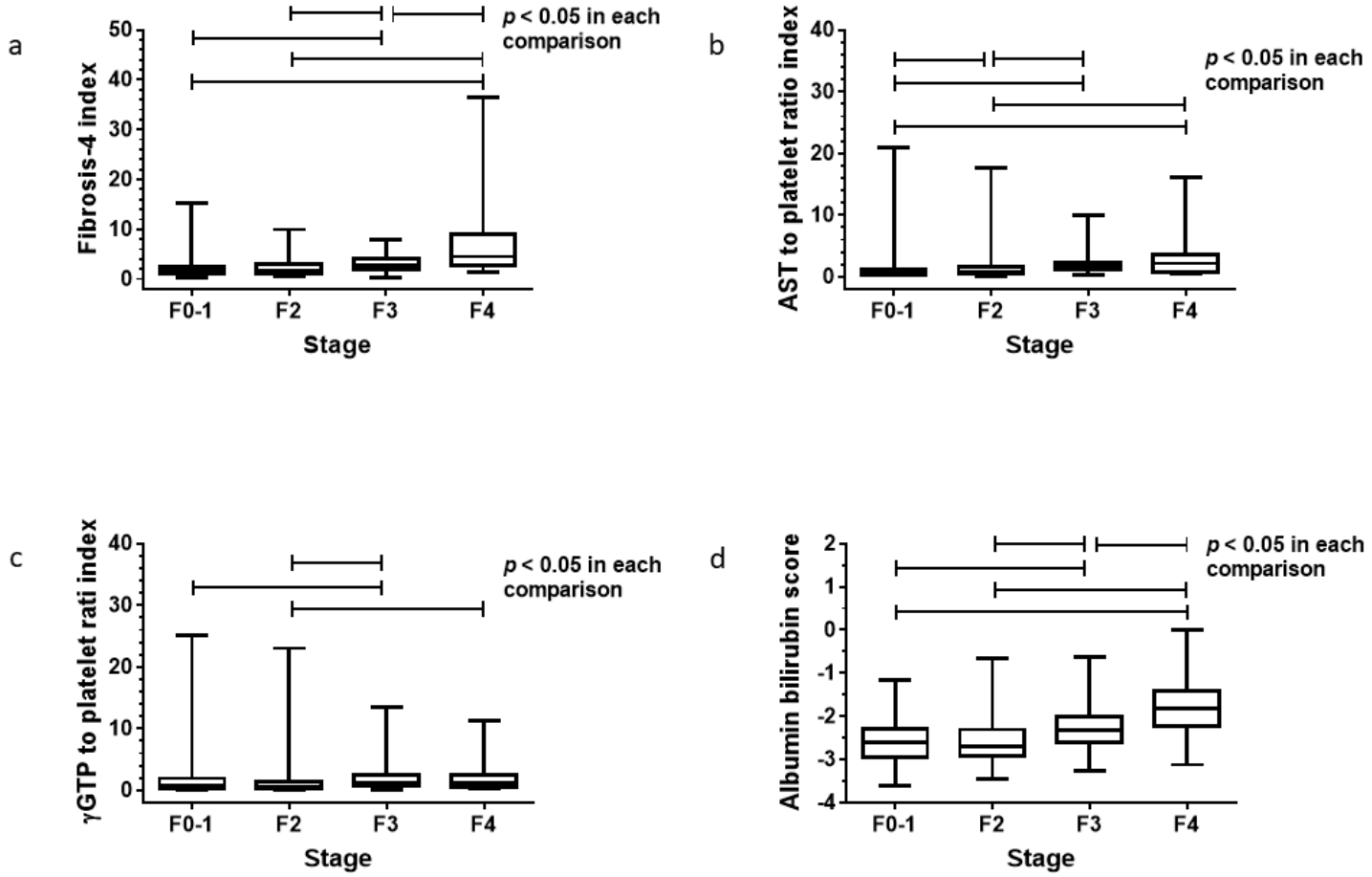
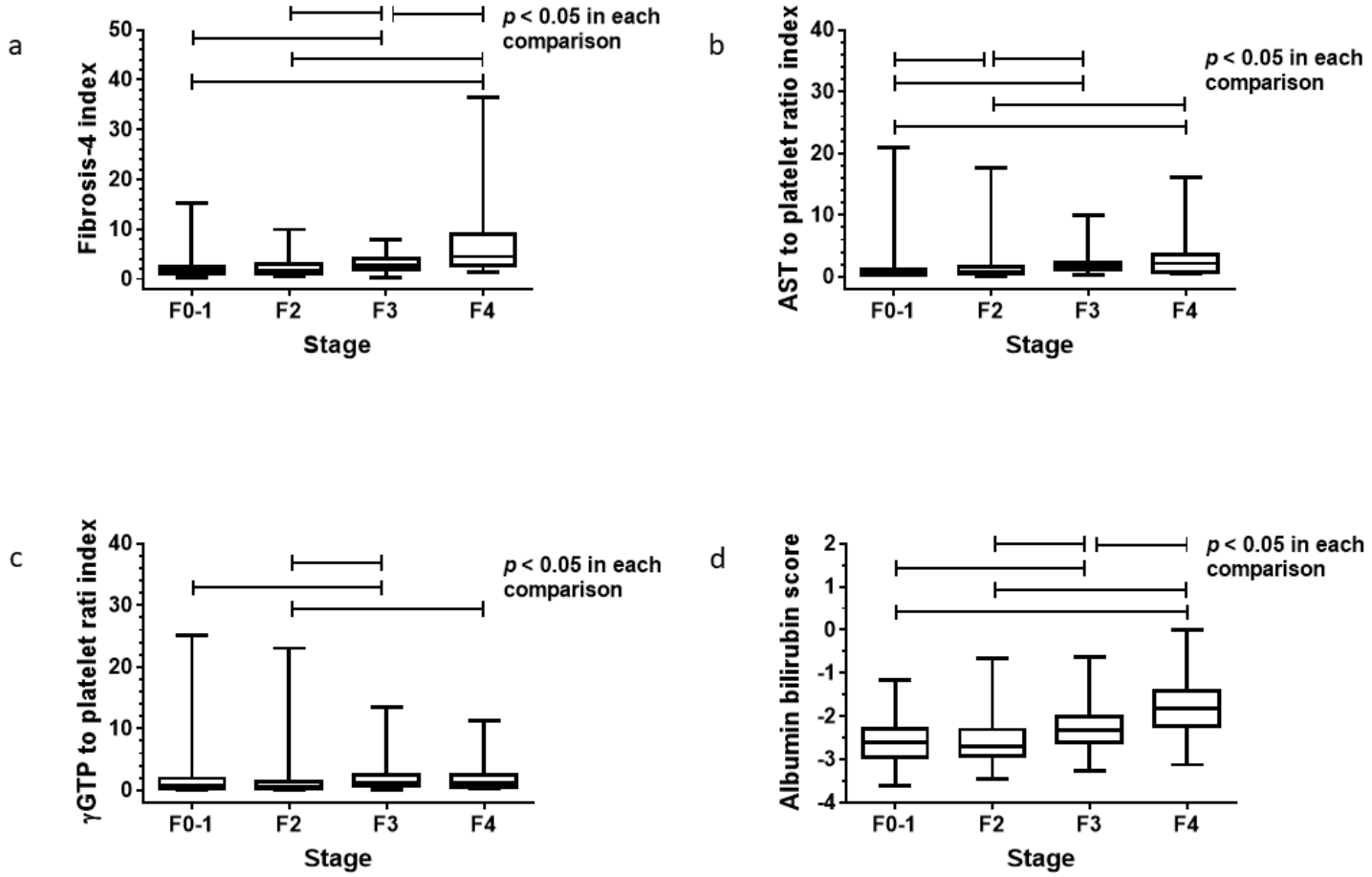


Figure 5

Conventional fibrosis indexes in each fibrosis stage in a training cohort FIB-4 (a) and ALBI score (d) differentiated fibrosis stage 3 from stage 2 and stage 4 from stage 3 whereas they failed to differentiate between F0-1 and 2 ($p < 0.05$). APRI (b) did not distinguish stage 4 from 3. GPR (c) was not significantly different between F0-1 and 2 and between F3 and 4. Data were analyzed using the Steel-Dwass test.



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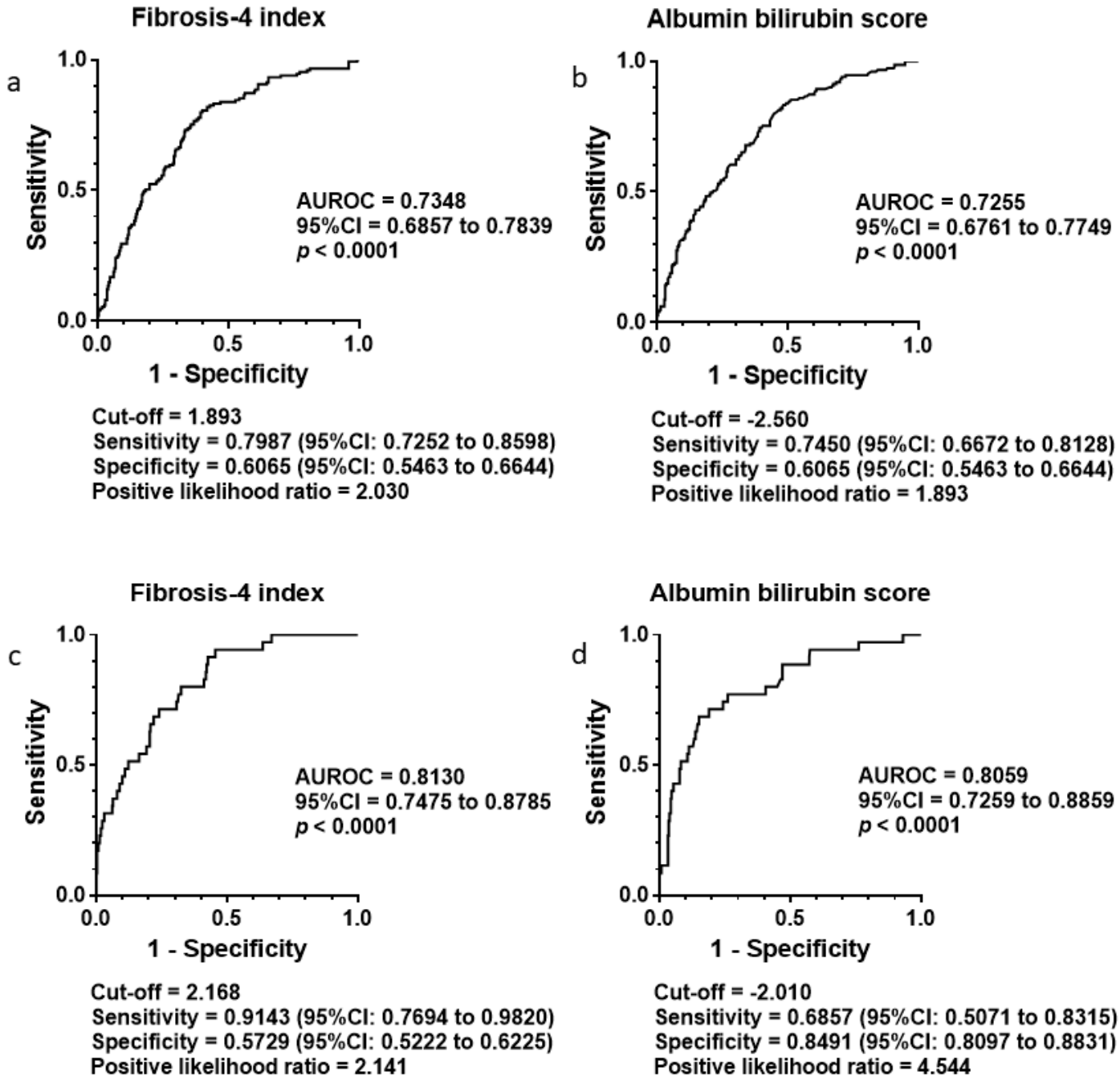
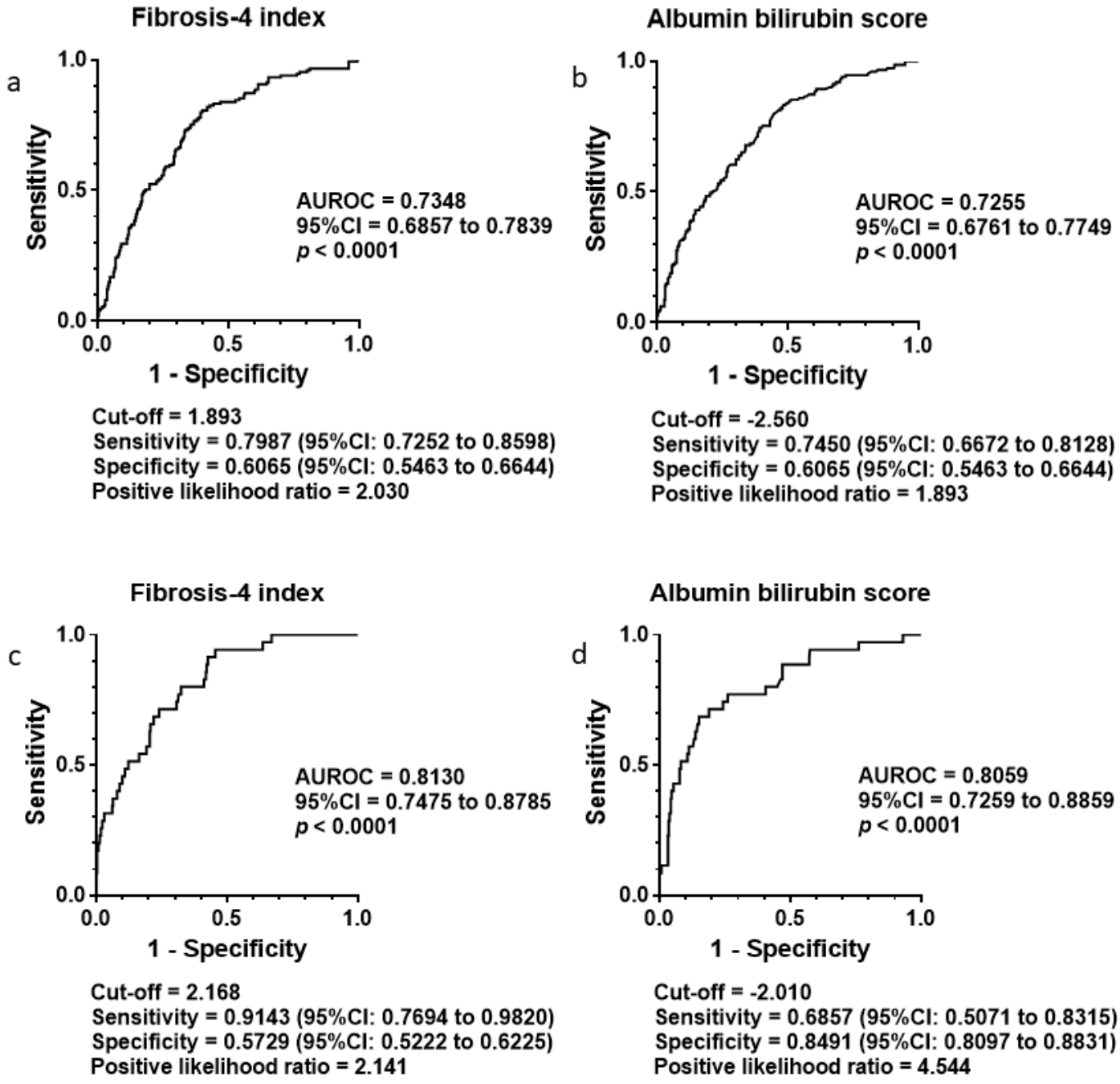


Figure 6

Differential diagnosis of liver fibrosis by Fibrosis-4 index and Albumin bilirubin score in a training cohort ROC analysis confirmed the ability of fibrosis indexes to differentiate advanced liver fibrosis (F3-4) from nonadvanced fibrosis (F1-2) by Fibrosis-4 index (a) and ALBI score (b). Cirrhosis was also differentiated from noncirrhotic status by both of indexes (c, d). P values less than 0.05 were considered statistically significant.



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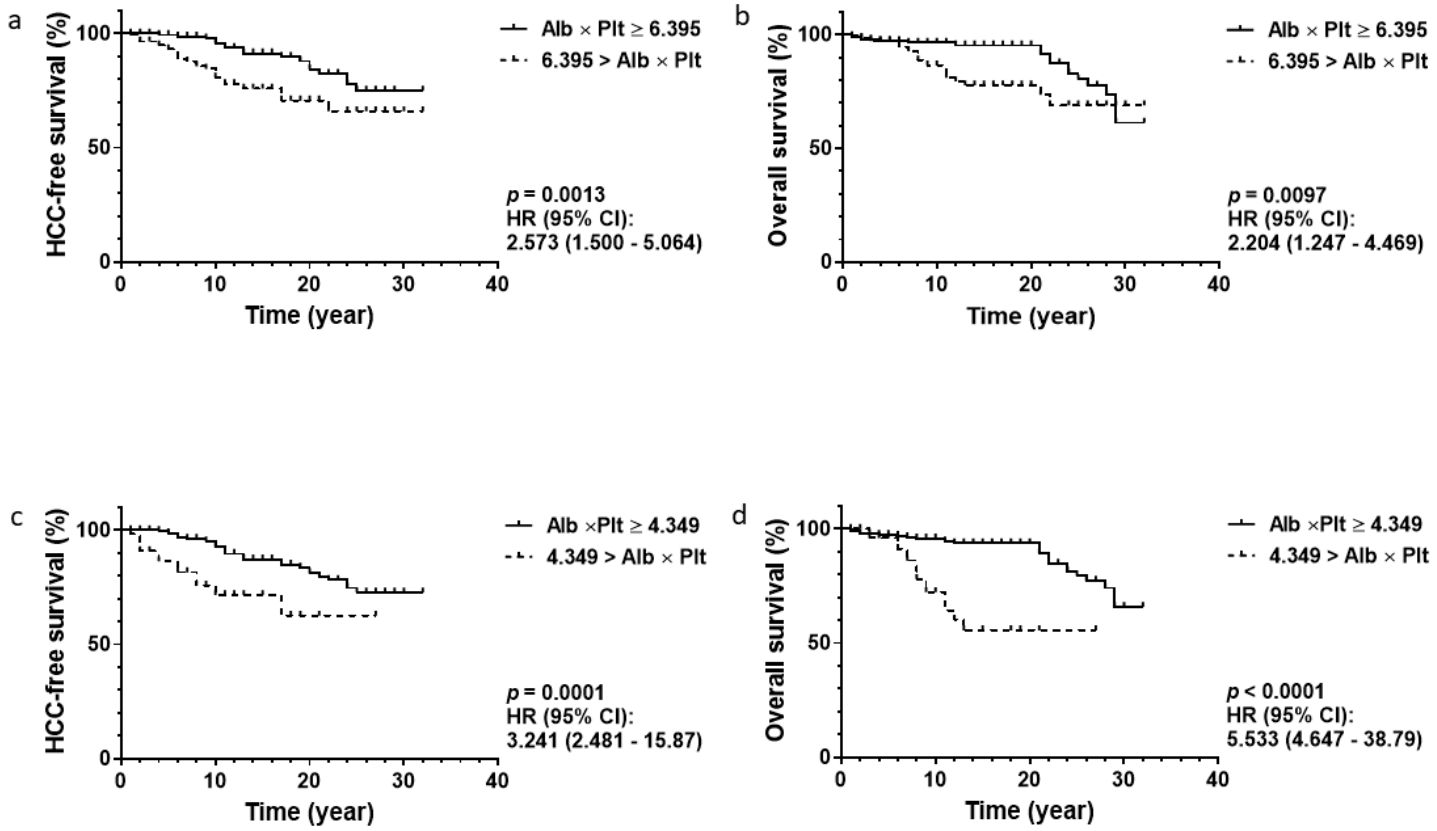
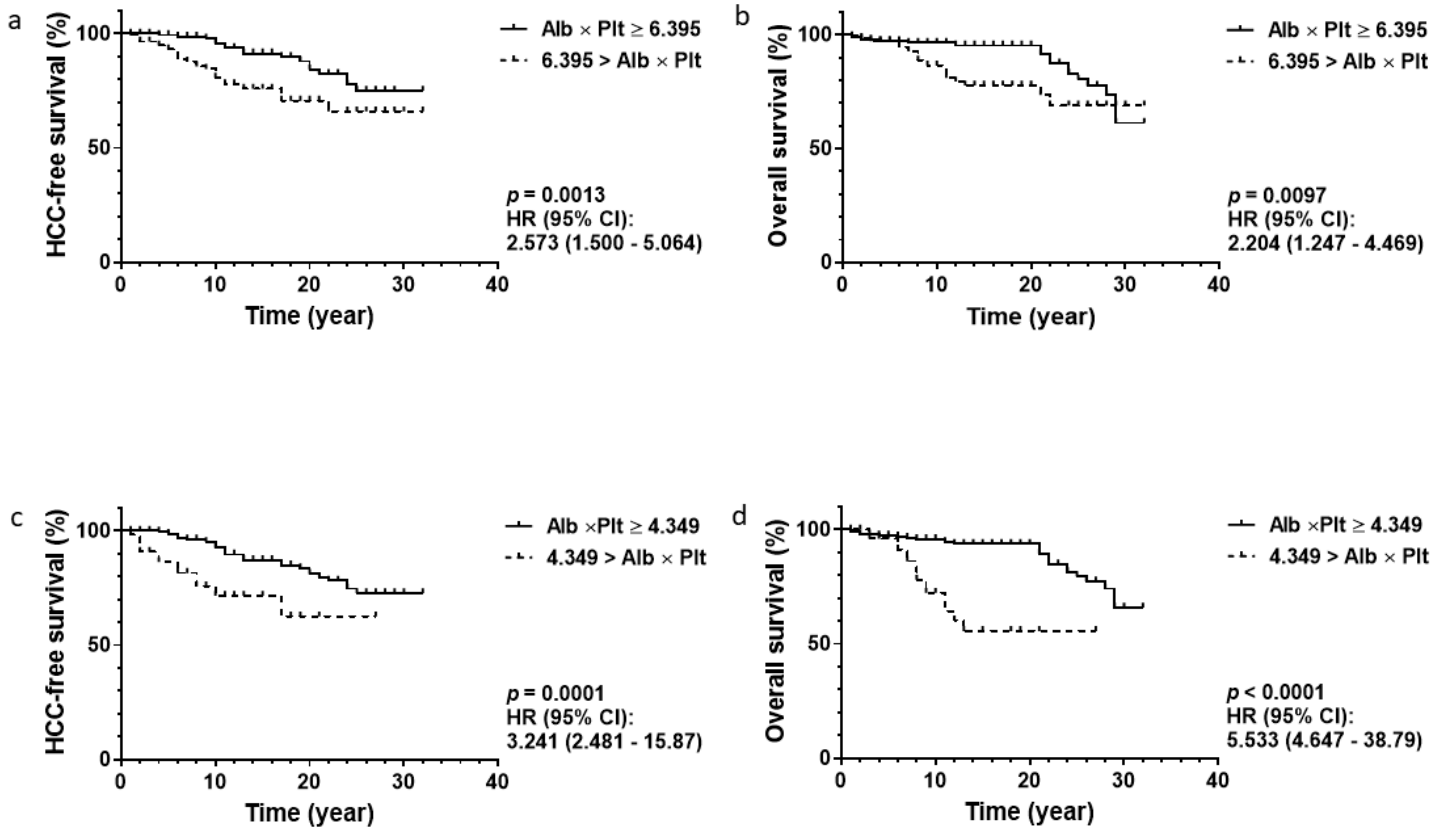


Figure 7

HCC-free survival and overall survival in a training cohort Among 336 patients followed up for at least 1 year, 45 patients were complicated with HCC and 42 patients died. An Albumin platelet product cut-off value = 6.395 could differentiate HCC-free survival (a) and overall survival (b) in the Kaplan-Meyer analysis. Albumin platelet product = 4.349 also predicted a difference in HCC-free survival (c) and overall survival (d) with statistical significance. P values less than 0.05 were considered statistically significant.



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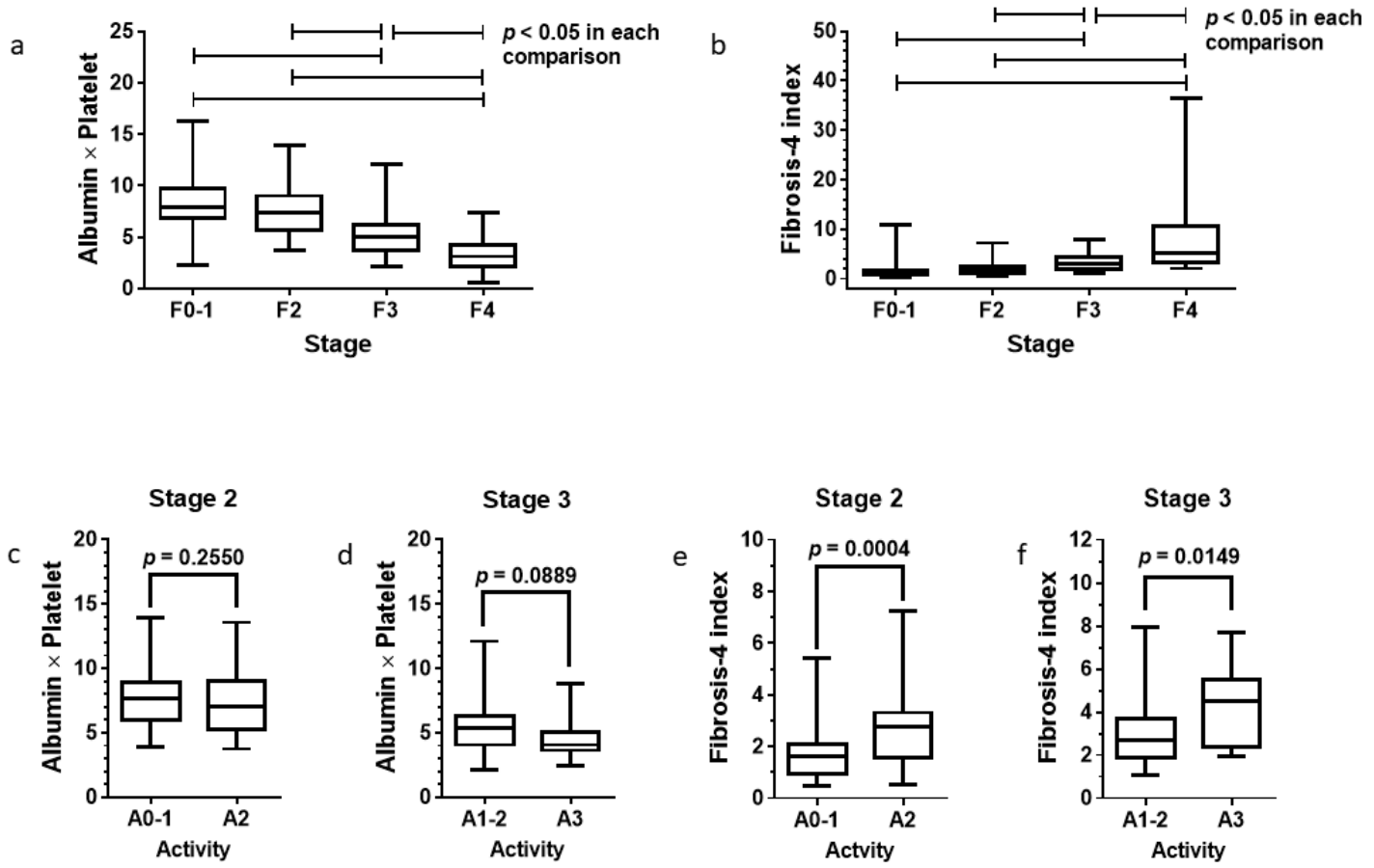
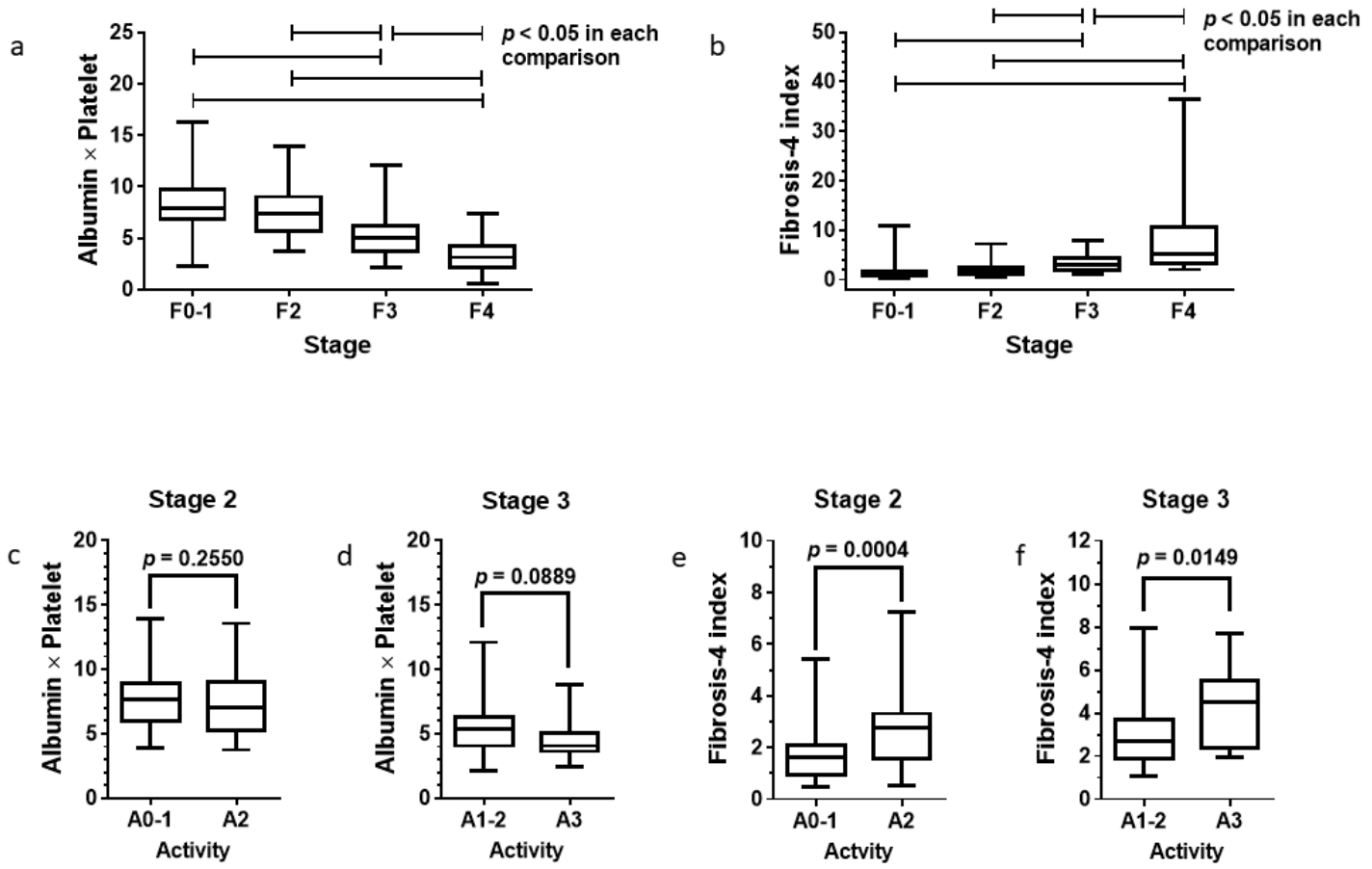


Figure 8

Fibrosis staging of HCV patients in a training cohort Albumin platelet product (a) and Fibrosis-4 index (b) divided stage 3 from stage 2. Albumin platelet product in fibrosis stage 2 was not statistically different between activity grade 0-1 group and grade 2 group (c). In stage 3, Albumin platelet product for grade 3 group did not differ from that of grade 1-2 group (d). In case of Fibrosis-4 index, the median values were significantly different depending on activity grade in stage 2 (e) and stage (f). Data were analyzed using the Steel-Dwass test or Mann-Whitney-U test. P values less than 0.05 were considered statistically significant.



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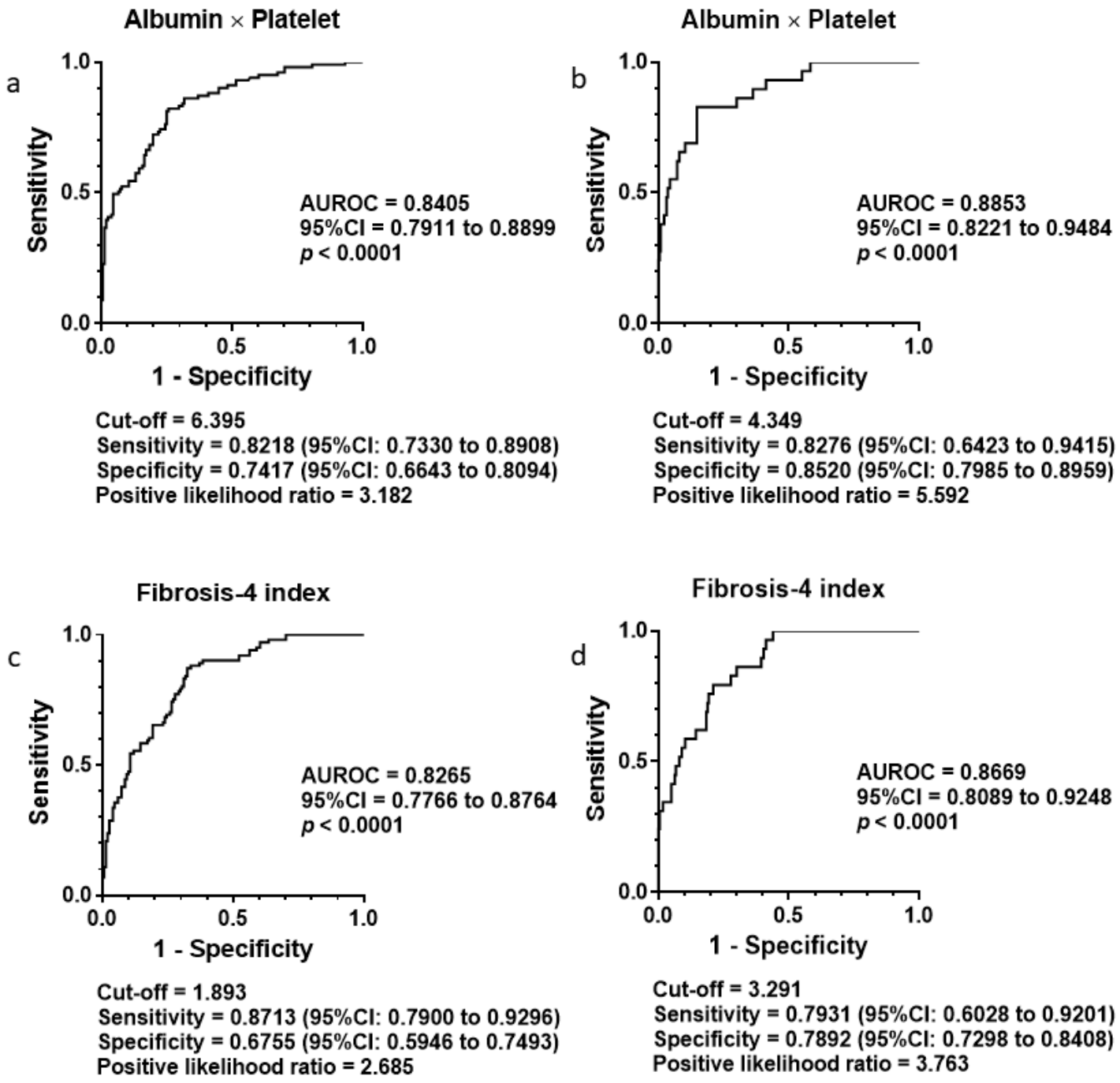
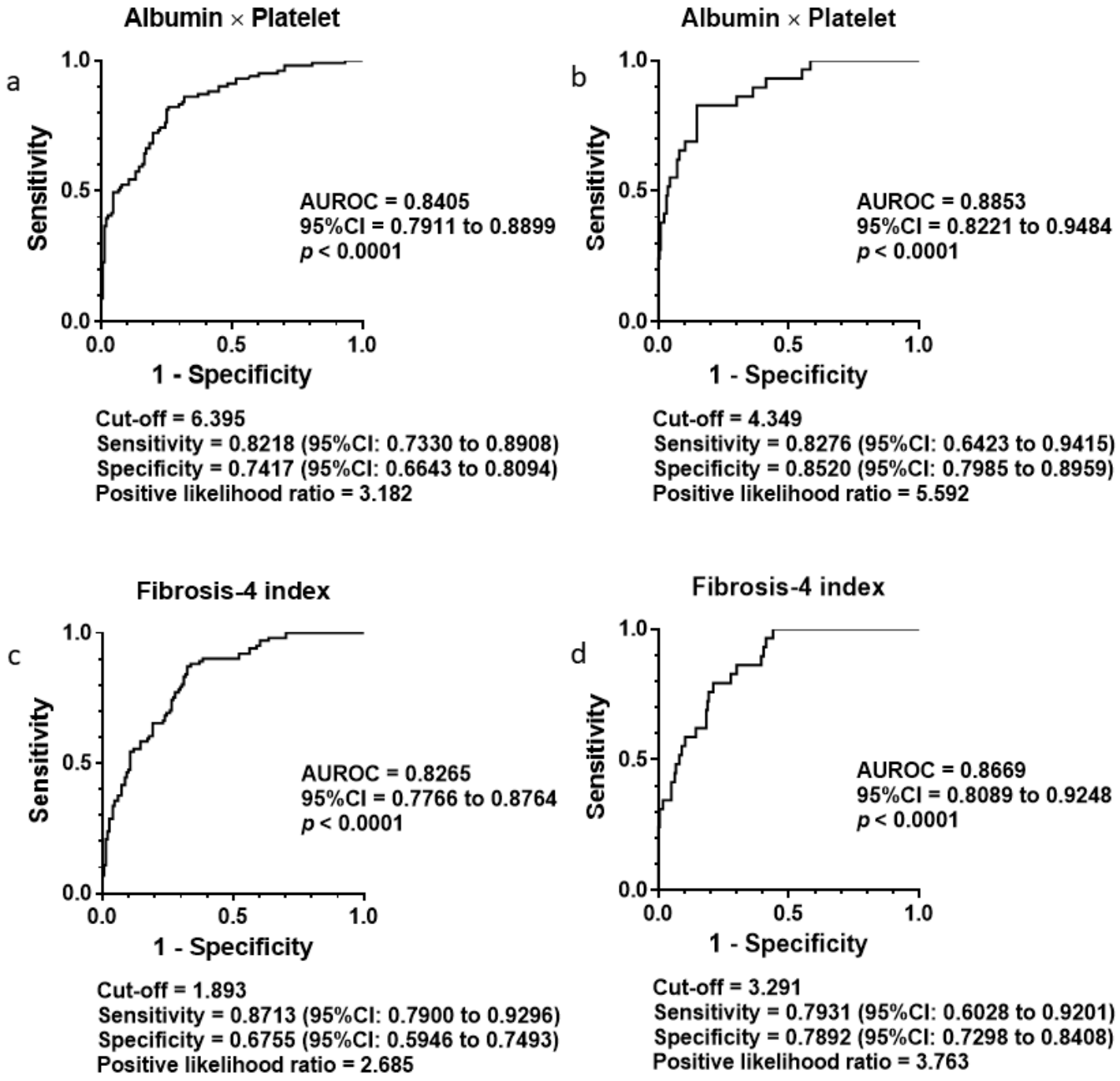


Figure 9

Differential diagnosis of liver cirrhosis by newly generated fibrosis indexes of HCV patients in the training cohort ROC analysis revealed that Albumin platelet product (a) differentially diagnosed advanced fibrosis (F3-4) from nonadvanced fibrosis (F0-2) and cirrhosis from noncirrhotic status (b). Two cut-off values determined by Youden index were identical to those in the training cohort. Fibrosis-4 index also distinguished F3-4 from F0-2 (c) and F4 from F0-3 (d). AUROCs were greater in Albumin platelet product compared to Fibrosis-4 index. P values less than 0.05 were considered statistically significant.



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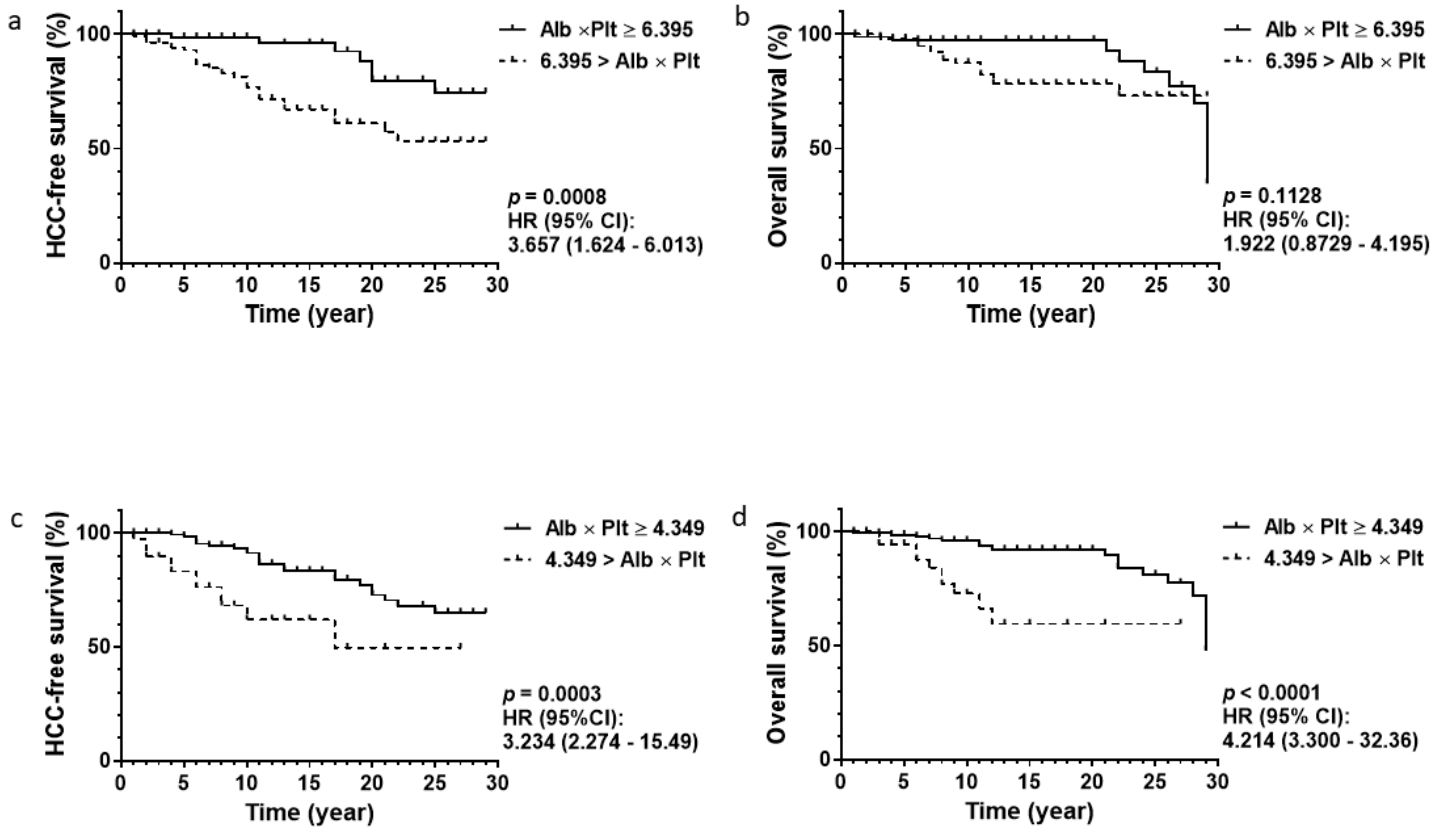
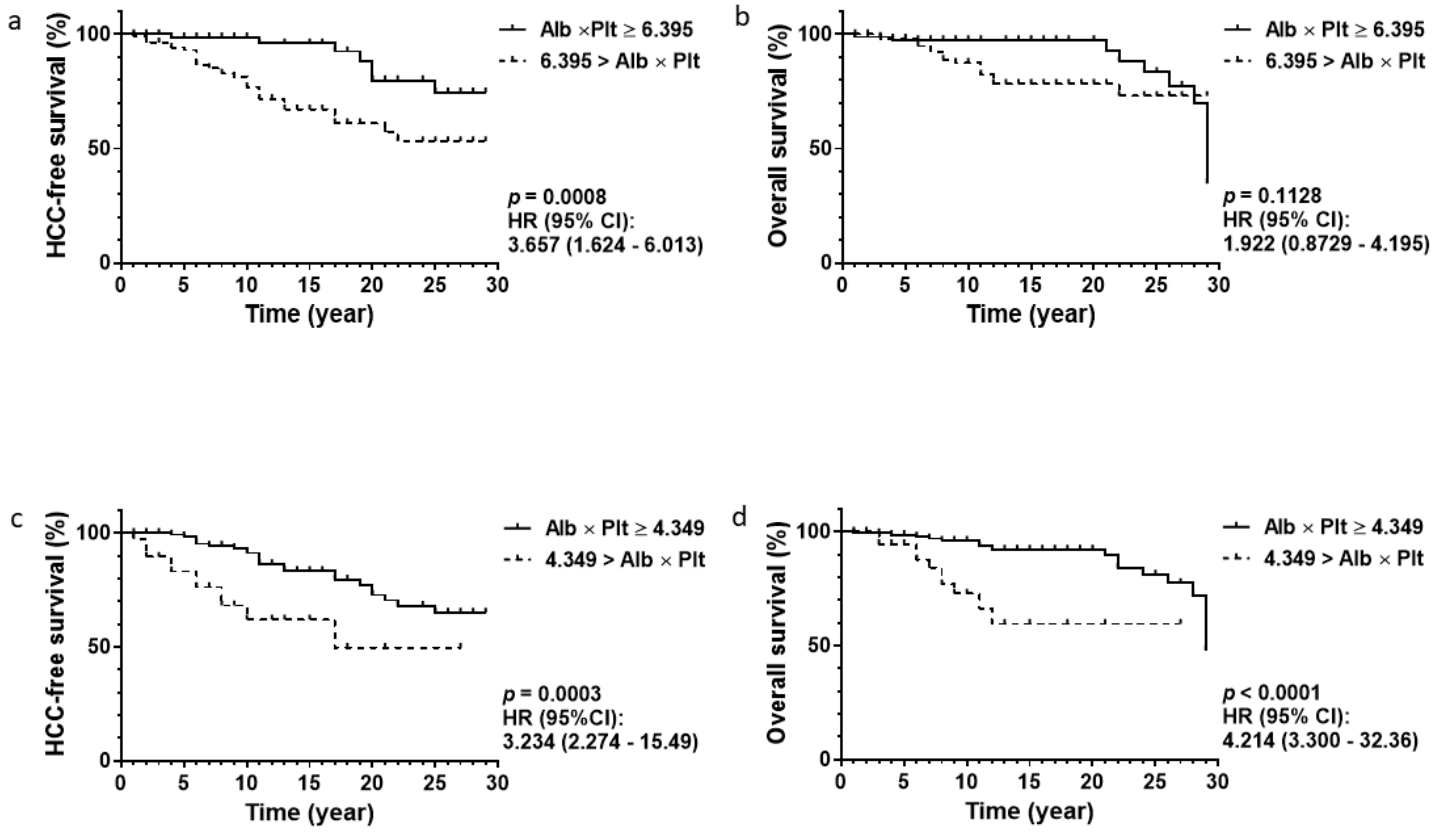


Figure 10

HCC-free survival and overall survival of HCV patients in a training cohort Among 191 patients followed up at least 1 year, 37 patients were complicated with HCC and 25 ones died. Kaplan-Meyer analysis revealed that a cut-off value of Albumin platelet product = 6.395 differentiated HCC-free survival (a), but it failed in overall survival (b). Albumin platelet product = 4.349 predicted difference of HCC-free survival (c) and overall survival (d) with statistical significance. P values less than 0.05 were considered statistically significant.



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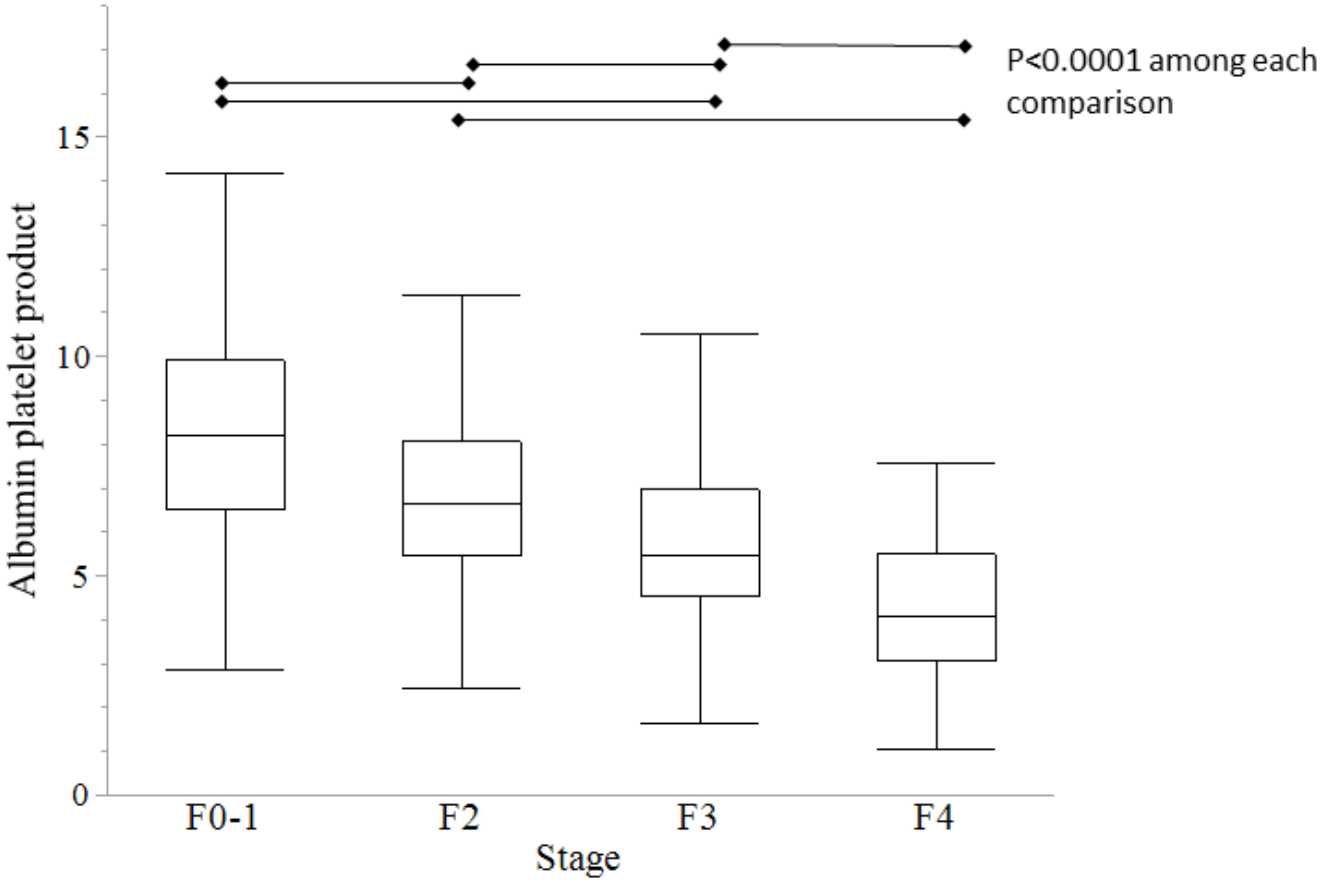
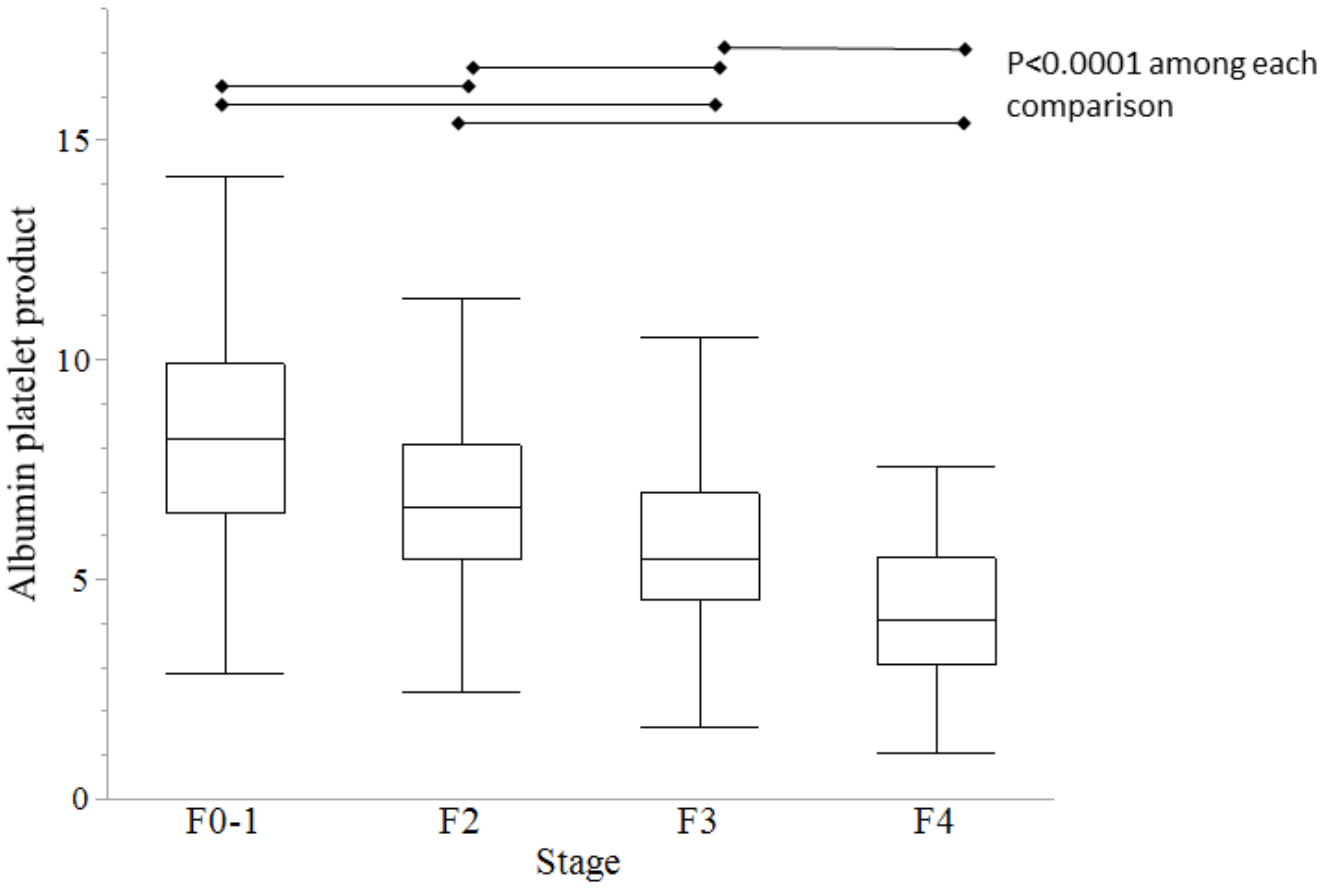


Figure 11

Fibrosis staging by the Albumin platelet product in a validation cohort The Albumin platelet product could significantly differentiate stages 0-1, 2, 3, and 4. Data were analyzed using the Steel-Dwass test. P values less than 0.05 were considered statistically significant.



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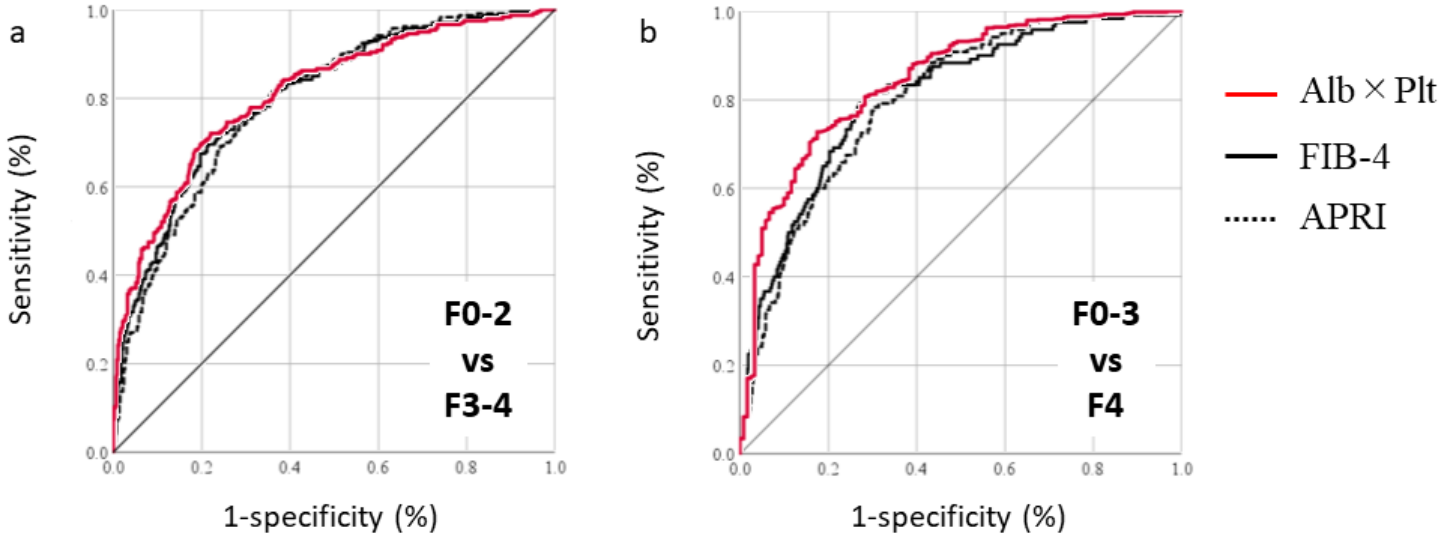
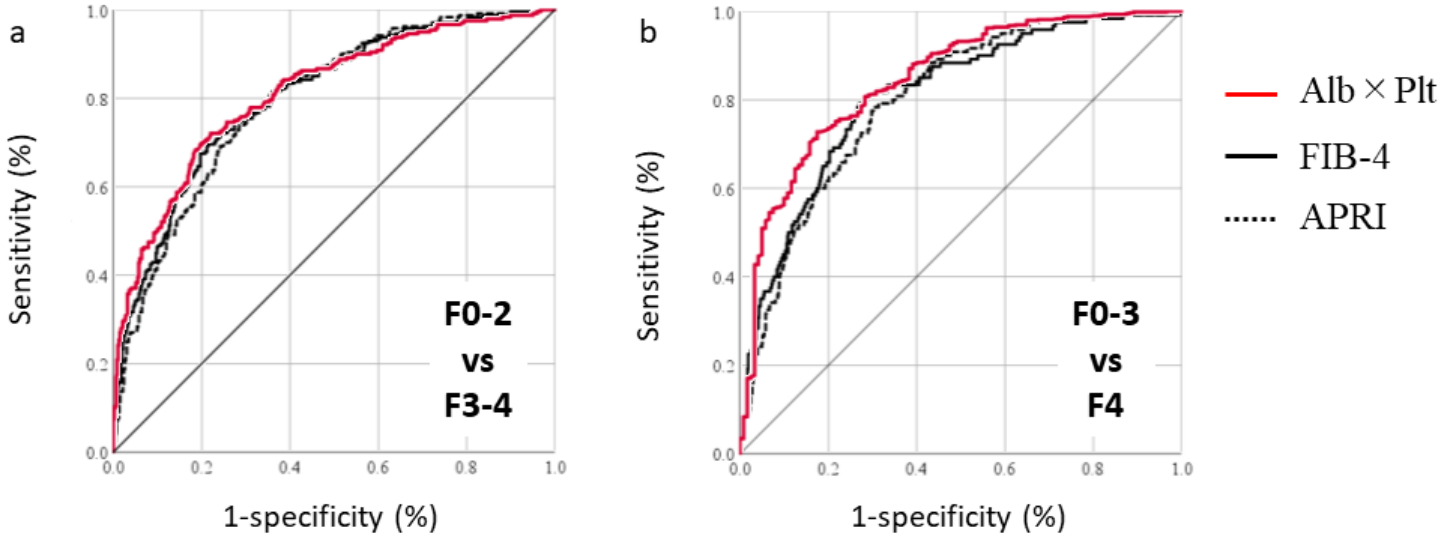


c

AUROC	F0-2 vs F3-4 (n) (467) (240)	F0-3 vs F4 (n) (587) (120)
Alb × Plt	0.812 (95%CI: 0.778 – 0.846)	0.846 (95%CI: 0.808 – 0.885)
FIB-4	0.804 (95%CI: 0.770 – 0.838)	0.810 (95%CI: 0.769 – 0.852)
APRI	0.794 (95%CI: 0.761 – 0.828)	0.802 (95%CI: 0.762 – 0.842)

Figure 12

Differential diagnosis of liver fibrosis by the Albumin platelet product in a validation cohort ROC analysis was performed to evaluate diagnostic abilities of Albumin platelet product for advanced liver fibrosis (F3-4) from nonadvanced fibrosis (F0-2) (a); for cirrhosis from noncirrhotic status (F0-3) (b). Albumin bilirubin product yielded the largest area under curve among three indices; Albumin bilirubin product, Fibrosis-4 index and APRI (c).



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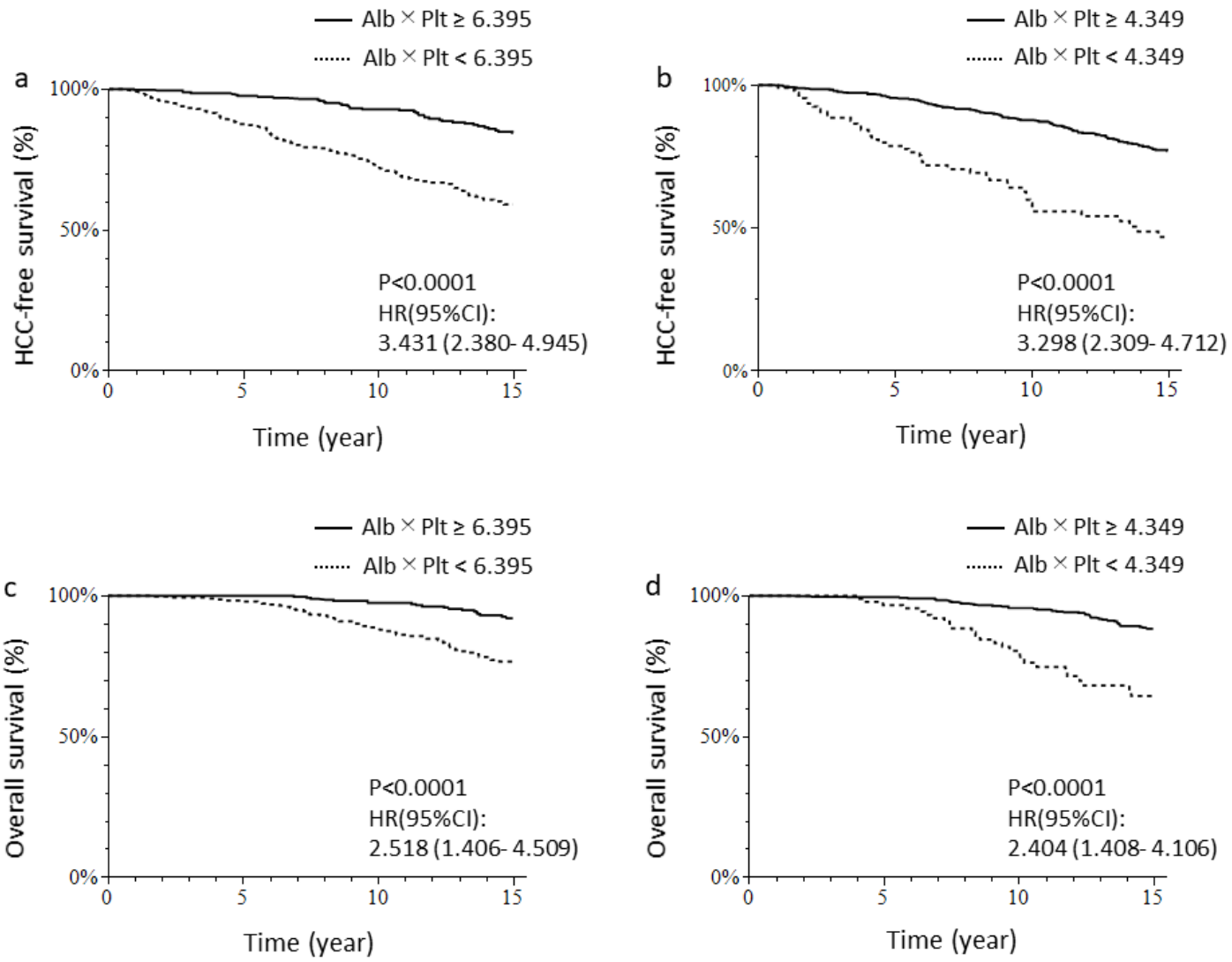
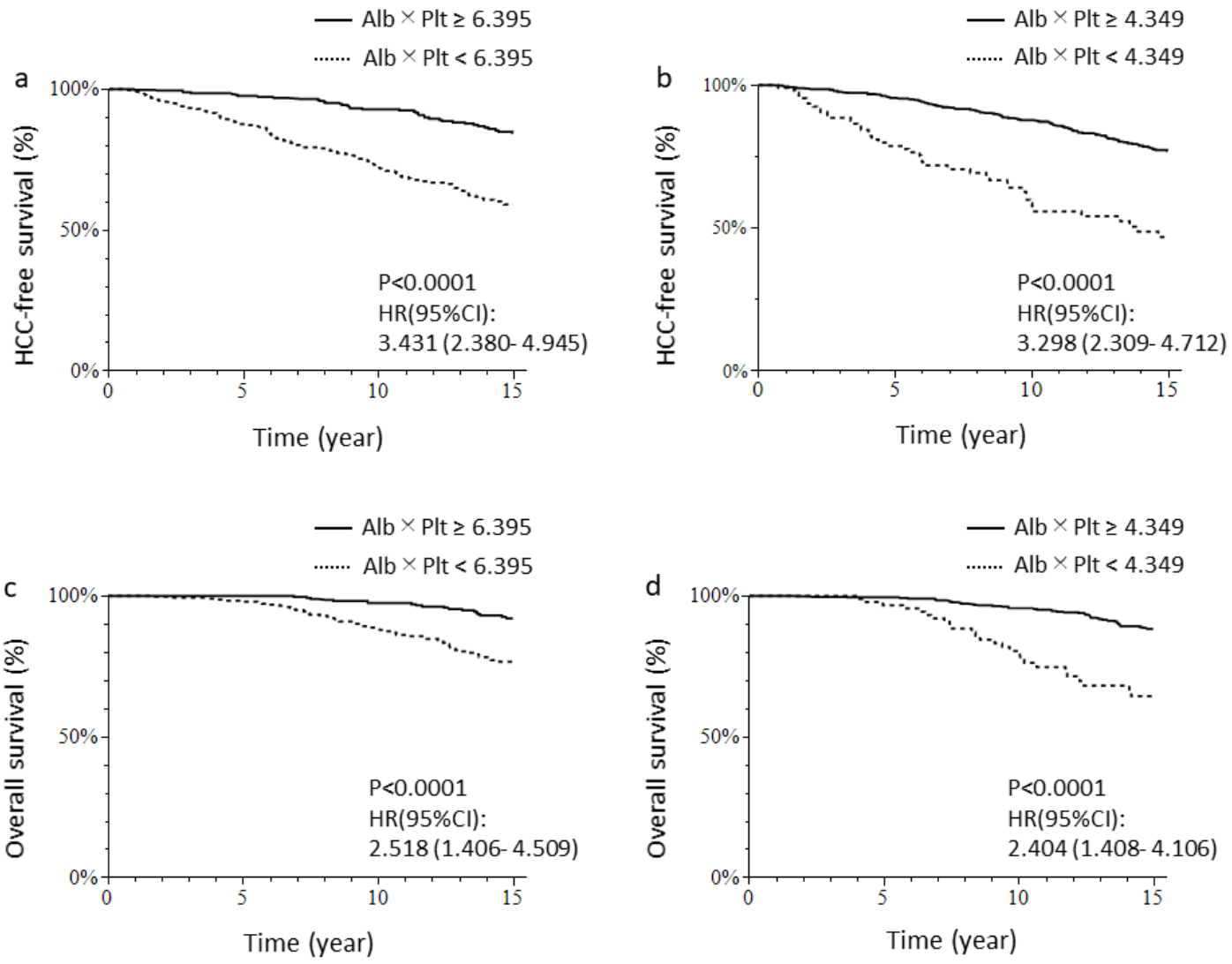


Figure 13

HCC-free survival and overall survival of patients with HCV infection in a validation cohort A validation cohort was divided by a cut-off value = 6.395 and = 4.349. HCC-free survival was significantly differentiated by Albumin platelet product = 6.395 (a) and = 4.349 (b). Two cut off values also stratified overall survival with statistical significance (c, d). P values less than 0.05 were considered statistically significant.



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