Fasting plasma lactate: A diagnosis and staging biomarker with superior performance in adult nonalcoholic fatty liver disease

Nie Xin
Sichuan University
E Jianfei
People's Hospital of Deyang City
He He
Sichuan University
Ding Fei
Sichuan University
Song Haolan
Sichuan University
Liu Qianhui
Sichuan University
Yin Mengting
Sichuan University
He Yong
Sichuan University
Li Guixing (liguixing27@163.com)
Sichuan University

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Abstract

Purpose: For the assessment and staging of metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM), fasting plasma lactate (FPL) has been a useful marker. However, it has never been used to evaluate nonalcoholic fatty liver disease (NAFLD). Since NAFLD is one of the significant metabolic syndromes, we investigated whether FPL can be used as a biomarker for diagnosing and staging NAFLD.

Methods: A total of 102 patients who were diagnosed with NAFLD and 100 healthy control between October 2018 and September 2019 were enrolled in our study. We determined the levels of FPL, total cholesterol(TC), triglycerides (TG), high-density lipoprotein cholesterol(HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose (FPG), fasting insulin(FINS), and homeostasis model assessment of insulin resistance (HOMA-IR). We performedreceiver operating characteristic (ROC) analysis to evaluate their diagnostic performance.

Results: In NAFLD patients, we found FPL, ALT, AST, TG, FPG, FINS, and HOMA-IR levels to be elevated while HDL-C level was reduced ($P < 0.05$). FPL, FPG, FINS, and HOMA-IR levels were higher in mild NAFLD patients than moderate to severe ones ($P < 0.05$). For NAFLD diagnosis and staging, the areas under the ROC curve (AUC) of FPL were 0.973 and 0.999, making it clearly ($P < 0.05$) superior to other biomarkers.For diagnosing and staging NAFLD, the cutoff value of1.285 mmol/L and 2.370 mmol/L for FPL had the highest validity, respectively. The sensitivity, specificity, negative likelihood ratio (LR-), and positive likelihood ratio (LR+) were 87.25%, 98.00%, 0.13, and 43.63 for the diagnosis cutoff value and. 92.19%, 97.37%, 0.08, and 35.05 for staging, respectively.In addition, for NAFLD patients, FPL positively correlated with TG, FPG, FINS, and HOMA-IR ($P < 0.05$).

Conclusion: Thus, in adult NAFLD, FPL can be used as a diagnosis and staging biomarker with superior performance.

1. Introduction

As a leading liver disease globally, nonalcoholic fatty liver disease (NAFLD) is one of the fastest emerging metabolic syndrome manifestations [1, 2]. Affecting up to 30% of the world's adult population, NAFLD causes considerable liver-related and extrahepatic morbidity and mortality [3, 4].NAFLD has become a highly prevalent form of liver disease in recent years. In most developed countries, it is considered a significant risk factor for the development of cirrhosis, liver failure, and hepatocellular carcinoma [5]. Beyond the liver, NAFLD also has important implications for developing diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and chronic kidney disease [3, 6–8]. Worse still, the prevalence of NAFLD is presumed to be increasing worldwide [9, 10].As there are long-term health risks and lack of symptoms until the advanced stage of NAFLD is reached, early diagnosis and subsequent staging are important. Currently, the only clinical tool available for the diagnosis of pathological alterations in the liver is a biopsy. However, the procedure is painful and includes risk. Thus, there is a need to identify noninvasive biomarkers of steatosis [11].

Traditionally, blood lactate (BL) concentrations were used as an index to reflect exercise intensity or as an indicator to find the severity of acute illnesses or injuries such as shock, sepsis, burns, and malignancy [12, 13]. In recent years, for the assessment and staging of severe obesity, T2DM, and other metabolic syndrome expressions, more and more data have suggested that fasting plasma lactate (FPL) can also be considered a useful marker [13–16]. As a metabolic syndrome, obesity, T2DM, and insulin resistance (IR) are closely associated with NAFLD [17–20], a potential biomarker for its diagnosis and staging could be FPL. However, there has been no report on the relationship of FPL levels with NAFLD as far as we know. Thus, in adults with NAFLD, we analyzed FPL and evaluated its diagnostic and staging efficacy.

2. Materials And Methods

A total of 102 patients diagnosed with NAFLD between October 2018 and September 2019 at West China Hospital, Sichuan University, were included in this study. According to the guidelines of prevention and treatment for nonalcoholic fatty liver disease updated by the National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association in 2018, the diagnosis and staging of NAFLD is based on theUltrasound (US) [21, 22]. We also included 100 healthy volunteers in this study as controls.Following were the exclusion criteria: (1) patients with secondary liver damage caused by severe infection, surgery, trauma, etc.; (2) people with a history of alcohol overconsumption (≥ 210 g per week in men and ≥ 140 g per week in women during the past 12 months); (3)those who have any of the diseases that can cause liver fat deposition, e.g., viral hepatitis, autoimmune hepatitis, drug-induced liver disease, hepatolenticular degeneration, etc.; and (4)people with a history of taking hepatoprotective drugs, lipid-lowering drugs, or drugs that can cause liver fat deposition. We obtained signed informed consent from all participants or their guardians, and the Ethics Committee of West China Hospital, Sichuan University, approved the study, and all methods were performed in accordance with the relevant guidelines and regulations.

After avoiding a high-fat diet for 3 days, fasting blood samples of all subjects were collected. We obtained plasma samples for FPL and FPG tests from an anticoagulant tube with sodium fluoride using centrifugation at 1000g for 15 minutes. Serum samples for total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and fasting insulin (FINS) tests were obtained from avacuum tubewithout anticoagulant. By matching the reagent via a c702 Auto Biochemical Analyzer (Roche Diagnostics, Germany) and FINS via an e601 Automatic Electrochemiluminescence Analyzer (Roche Diagnostics, Germany), FPL, FPG, TC, TG, HDL-C, LDL-C, ALT, and AST were determined. Through FINS reading (μIU/mL) multiplied by FPG concentration (mmol/L) and divided by 22.5 [23], we performed a homeostasis model assessment of insulin resistance (HOMA-IR).

We expressed basic information and laboratory parameters as the number, means ± standard deviation, or median (interquartile range) and compared these by the chi-square test, Student's *t-test*, or Wilcoxon rank-sum test. We used the Pearson correlation analysis to analyze the correlation between FPL and other laboratory parameters. For all analyses, P 0.05 was considered significant. All statistical computations were performed by SPSS 20.0 (SPSS Inc., Chicago, IL, USA). We used the SigmaPlot 14.0 to plot receiver-operating characteristic (ROC) curves (Systat Software Inc, California, USA). We compared the area under the curve (AUC) by thesoftware using the Mann–Whitney *U* Test ($U = (AUC_1\text{-}AUC_2)/(\text{Standard Error } AUC_1^2 + \text{Standard Error } AUC_2^2)$ ^ (1/2)). From the ROC curves, the FPL cut-off value was obtained, and according to the principle of maximizing Youden's index, the sensitivity and specificity were calculated (sensitivity + specificity − 1). We also computed the positive likelihood ratio (LR+) and the negative likelihood ratio (LR−).

3. Results

3.1 Biochemical characteristics of NAFLD patients

Biochemical characteristics of 102 NAFLD patients and 100 healthy controls are shown in **Table 1**. Compared to controls, NAFLD patients had elevated FPL, ALT, AST, TG, FGB, FINS, and HOMA-IR, while lower HDL-C. Between the two groups, no significant difference ($P > 0.05$) was found in TC and LDL-C as well as age and gender.

Among the NAFLD patients, 64 were mild, and 38 were moderate to severe. In moderate to severe patients, FPL, FPG, FINS levels, and HOMA-IR were significantly higher than in mild patients ($P < 0.05$), while ALT, AST, TG, TC, HDL-C, and LDL-C levels of the two did not differ ($P > 0.05$) **(Table 2)**.

3.2 FPL, ALT, AST, TG, HDL-C, FPG, FINS, and HOMA-IR for NAFLD diagnosing

For NAFLD diagnosing, AUC (95% confidence interval (CI), $P < 0.0001$ against the AUC 0.5 line) of FPL was 0.973 (0.956 to 0.990), ALT was 0.810 (0.751 to 0.868), AST was 0.815 (0.755 to 0.875), TG was 0.828 (0.772 to 0.884), -HDL-C (HDL-C multiplied by -1) was 0.851 (0.797 to 0.9055), FPG was 0.812 (0.753 to 0.872), FINS was 0.915 (0.876 to 0.953), and HOMA-IR was 0.930 (0.897 to 0.963) **(Figure 1A–H)**. The AUC of FPL was clearly (P < 0.05) superior to others **(Table 3)**. According to the principle of maximizing Youden's Index (sensitivity + specificity - 1), in diagnosing NAFLD, the cutoff value of 1.285mmol/L of FPL had the highest validity. For this cutoff value, the sensitivity was 87.25%, specificity was 98.00%, LR- was 0.13, and LR+ was 43.63.

3.3 FPL, FPG, FINS, and HOMA-IR for NAFLD staging

For NAFLD staging, AUC (95% confidence interval (CI), *P* against the AUC 0.5 line) of FPL, FPG, FINS, and HOMA-IR (to distinguish mild from moderate to severe) were 0.999 (0.997 to 1.000, $P < 0.0001$), 0.709 (0.605 to 0.813, $P = 0.0004$), 0.929 (0.870 to 0.988, $P < 0.0001$), and 0.962 (0.9140 to 1.009, $P < 0.0001$), respectively **(Figure 2A–D)**. **Table 4** shows the difference between the AUCs. The AUC of FPL was superior to those of FPG ($P < 0.0001$) and FINS ($P = 0.0198$) but did not differ from that of HOMA-IR ($P = 0.1207$). The cutoff value of FPL at 2.370 mmol/L had the highest validity in NAFLD staging. For this cutoff value, the sensitivity was 100.00%, specificity was 97.37%, LR- was 0.00, and LR+ was 38.02. The cutoff value of HOMA-IR at 4.35 had the highest validity in NAFLD staging. For this cutoff value, the sensitivity was 92.19%, specificity was 97.37%, LR- was 0.08, and LR+ was 35.05.

3.4 The association of FPL with other biochemical characteristics in NAFLD patients

The association of FPL with other biochemical parameters in NAFLD patients is shown in **Table 5**. As suggested by the Pearson correlation analysis, FPL of NAFLD patients positively correlated with TG, FPG, FINS, and HOM-IR ($r = 0.233$, 0.405, 0.825, and 0.897, $P < 0.05$).

4. Discussion

This is the first study where the FPL level has been detected in NAFLD patients, and its clinical utility in diagnosing and staging the disease has been assessed. Our results indicate that the FPL level is elevated in NAFLD patients, with an ideal cutoff value of 1.285 mmol/L and 2.370 mmol/L, respectively.

In general, although NAFLD as a whole is characterized by disease progression, the actual progression and the rate at which disease progression occurs in all populations are still unclear. It is thus important to diagnose and stage the disease effectively. For the assessment of inflammation and fibrosis, liver biopsy is the gold standard test, but it is not suited for routine NAFLD screening being an invasive procedure.With increasing availability and accuracy, noninvasive approaches including serum biomarkers and imaging modalities have come to the clinical forefront [24]. Liver function tests and lipid profile have been done routinely in a clinical laboratory to assist in diagnosing NAFLD [1, 25-27]. ALT is the most commonly used among these. Previous studies have mentioned that elevated ALT levels correlate with NAFLD and advanced fibrosis, but patients with normal ALT may also have NAFLD and advanced fibrosis. Other liver function biomarkers and lipid profiles have shown even lower prognostic value [28-30]. In this study, we found that ALT, AST, TG, and HDL-C levels in NAFLD patients increased or decreased significantly compared to healthy controls but showed no difference between mild NAFLD patients and moderate to severe ones. It reflected the relatively poor sensitivity and specificity of using these biomarkers in NAFLD-related diagnosis and disease staging, thus emphasizing the importance of developing improved biomarkers for more accurate disease monitoring and prognosis.

We have found evidence on the links between NAFLD pathogenesis and metabolic dysfunction such as IR, T2DM, and obesity [17-20]. Hence, it is not surprising that FPG, FINS, and HOMA-IR were associated with NAFLD and its severity. We found that FPL increased not only in NAFLD patients compared to healthy controls, but it also related to the severity of the disease. In addition, FPL was the best biomarker for NAFLD diagnosis and staging with superior performance, as indicated in the ROC analysis.However, the underlying mechanism is still unclear. More and more studies have suggested that FPL also can be considered a useful predictor of metabolic disease [13-16]. FPL concentrations were elevated in obesity and yet higher in type 2 diabetics compared to lean controls subjects.Among non-diabetics,elevated FPL was also associated with higher TG, lower HDL-C, and higher FPG. It is considered that elevated FPL is likely related to increased production by increased anaerobic glycolysis due to depressed oxidation of glucose and fatty acids [14]. FPL of NAFLD patients was positively correlated with TG, FPG, FINS, and HOM-IR as suggested in the Pearson correlation analysis. Thus, the FPL level changes of NAFLD patients may also be closely related to increased anaerobic glycolysis.

Following are the limitations of this study that need to be considered. First, the sample size was relatively small. Further studies with bigger numbers are warranted.

Second, this study was a cross-sectional design, and thus our findings should be validated in long-term prospective studies. Third, most patients enrolled in this study were diagnosed and staged by B-ultrasound without a liver biopsy. This may lead to bias in results. Thus, to confirm the association between FPL concentrations and liver biopsy, further studies are required.

Conclusion

In conclusion, FPL is a more useful diagnosing and staging marker for NAFLD in adults than other biochemistry indicators such as ALT, AST, TG, HDL-C, FPG, FINS, and HOMA-IR.Thus, in assisting NAFLD diagnosis and staging,FPL can be used as a helpful indicator.

Declarations

Ethics approval and consent to participate

Authors of this manuscript certify that every comply with the ethical guidelines for authorship. We obtained signed informed consent from all participants or their guardians, and the Ethics Committee of West China Hospital, Sichuan University, approved the study, and all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Written informed consents for publication were obtained from all participants.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author`s contributions

All authors participated in the study. Nie Xin and E Jianfei wrote the main manuscript; Ding Fei, Song Haolan, and Liu Qianhui prepared tables1-5; Yin Mengting and He He prepared figures 1-2; He Yong and Li guixing reviewed the manuscript and conceptualization. All authors have reviewed and approved the final version of the manuscript.

Competing interests

All authors declare that there is no conflict of interest.

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Tables

Table 2. Biochemical characteristics of mild and moderate to severe non-alcoholic fatty liver disease patients

	Mild patients	Moderate to severe patients	*P* value
Total number	64	38	/
FPL(mmol/L))	1.50（1.32,1.80）	2.84（2.53,3.48）	0.000*
ALT(U/L)	40（25,53）	45（29,58）	0.286
AST(U/L)	26（23,33）	30（26,35）	0.215
TG(mmol/L)	1.58（1.29,2.51）	2.03(1.35,2.92)	0.258
TC(mmol/L)	4.69（4.20,5.38）	4.86(4.45,5.38)	0.406
HDL-C(mmol/L)	1.10（0.98,1.30）	1.11(0.97,1.32)	0.959
LDL-C(mmol/L)	2.81（2.33,3.26）	2.88(2.33,3.67)	0.611
FPG(mmol/L)	5.40（5.08,5.90）	6.01(5.57,6.58)	0.000*
FINS(mIU/L)	12.68（9.78,15.32）	22.82(19.11,27.20)	0.000*
HOMA-IR	3.06（2.39,3.78）	5.80(5.03,6.93)	0.000*

Note:The biochemical characteristics were expressed as median (interquartile range). FPL: fasting plasma lactate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance. *P<0.05.

Table 1. Biochemical characteristics of non-alcoholic fatty liver disease patients and healthy controls

	NAFLD patients	Controls	P value
Total number	102	100	/
Age	43±12	44±11	0.852
Gender			0.944
Male	80(78%)	80(80%)	
Female	22(22%)	20(20%)	
FPL(mmol/L))	1.96（1.44,2.65）	0.84（0.75,1.15）	0.000*
ALT(U/L)	42（25,55）	19（13,27）	0.000*
AST(U/L)	27（23,34）	19（16,22）	0.000*
TG(mmol/L)	1.82（1.30,2.79）	1.06（0.79,1.30）	0.000*
TC(mmol/L)	4.80±0.86	4.61±0.62	0.108
HDL-C(mmol/L)	1.18±0.33	1.66±0.35	0.000*
LDL-C(mmol/L)	2.86±0.85	2.67±0.56	0.065
FPG(mmol/L)	5.53（5.16,6.17）	4.93（4.68,5.21）	0.000*
FINS(mIU/L)	15.63（11.07,21.23）	6.62（5.18,9.10）	0.000*
HOMA-IR	4.01（2.65,5.20）	1.44（1.09,2.01）	0.000*

Note:The age, TC, HDL-C and LDL-C were expressed as means±standard deviation；The gender was expressed as n (%). The other biochemical characteristics were expressed as median (interquartile range).NAFLD: non-alcoholic fatty liver disease; FPL: fasting plasma lactate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; FINS:fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance. *shows P<0.05.

Table 3 Difference of the area under the ROC curves for non-alcoholic fatty liver disease diagnosing

	FPL	ALT	AST	TG	-HDL-C	FPG	FINS	HOMA-IR
FPL	□	0.163(0.102, 0.225) P< 0.0001□	0.158(0.094, 0.221) P< 0.0001□	0.145(0.087, 0.202) P< 0.0001□	0.122(0.067, 0.178) < 0.0001□	0.161(0.103, 0.219) P< 0.0001□	0.058(0.028, 0.089) P=0.0002□	0.043(0.018, 0.067) P=0.0006□
ALT	□	□	-0.006(-0.055, 0.043) P=0.8227	-0.019(-0.096, 0.059) P=0.6333	-0.041(-0.118, 0.036) P=0.2965	-0.003(-0.090, 0.084) P=0.9507	-0.105(-0.176, -0.034) P=0.0040□	-0.120(-0.190, -0.051) P=0.0006□
AST	□	□	□	-0.013(-0.095, 0.068) P=0.7501	-0.035(-0.115, 0.044) P=0.2822	0.003(-0.085, 0.091) P=0.9495	-0.099(-0.173, -0.026) P=0.0079□	-0.120(-0.190, -0.051) P=0.0016□
TG	□	□	□	□	-0.022(-0.086, 0.042) P=0.4941	0.016(-0.059, 0.091) P=0.6756	-0.086(-0.151, -0.021) P=0.0097□	-0.115(-0.186, -0.044) P=0.0011□
-HDL-C	□	□	□	□	□	0.038(-0.040, 0.117) P=0.3382	-0.064(-0.126, -0.002) P=0.0431□	-0.080(-0.137, -0.022) P=0.0070□
FPG	□	□	□	□	□	□	-0.118(-0.178, -0.058) P=0.0040□	-0.102(-0.172, -0.033) P=0.0001□
FINS	□	□	□	□	□	□	□	-0.016(-0.029, -0.002) P=0.021□
HOMA-IR	□	□	□	□	□	□	□	□

Note: Difference of the area under the ROC curves were expressed as difference (95% Confidence Interval). FPL: fasting plasma lactate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance. □ shows P<0.05.

Table 4 Difference of the area under the ROC curves for non-alcoholic fatty liver disease staging

	FPL	FPG	FINS	HOMA-IR
FPL	□	0.209(0.186, 0.394) P< 0.0001□	0.070(0.011, 0.129) P=0.0198□	0.038(-0.010, 0.085) P=0.1207
FPG	□	□	-0.220(-0.351, -0.089) P=0.0010□	-0.252(-0.372, -0.133) P<0.0001□
FINS	□	□	□	-0.033(-0.057, -0.009) P=0.0073□
HOMA-IR	□	□	□	□

Note: Difference of the area under the ROC curves were expressed as difference (95% Confidence Interval). FPL: fasting plasma lactate; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance. □shows P<0.05.

Table 5 The association of fasting plasma lactate with other biochemical parameters in non-alcoholic fatty liver disease patients

	r	*P*
ALT	0.088	0.380
AST	0.043	0.668
TG	0.233	0.018*
TC	0.003	0.976
HDL-C	-0.040	0.690
LDL-C	0.028	0.779
FPG	0.405	0.000*
FINS	0.825	0.000*
HOMA-IR	0.897	0.000*

Note: ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; FINS:fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance. *shows $P<0.05$.

Figures

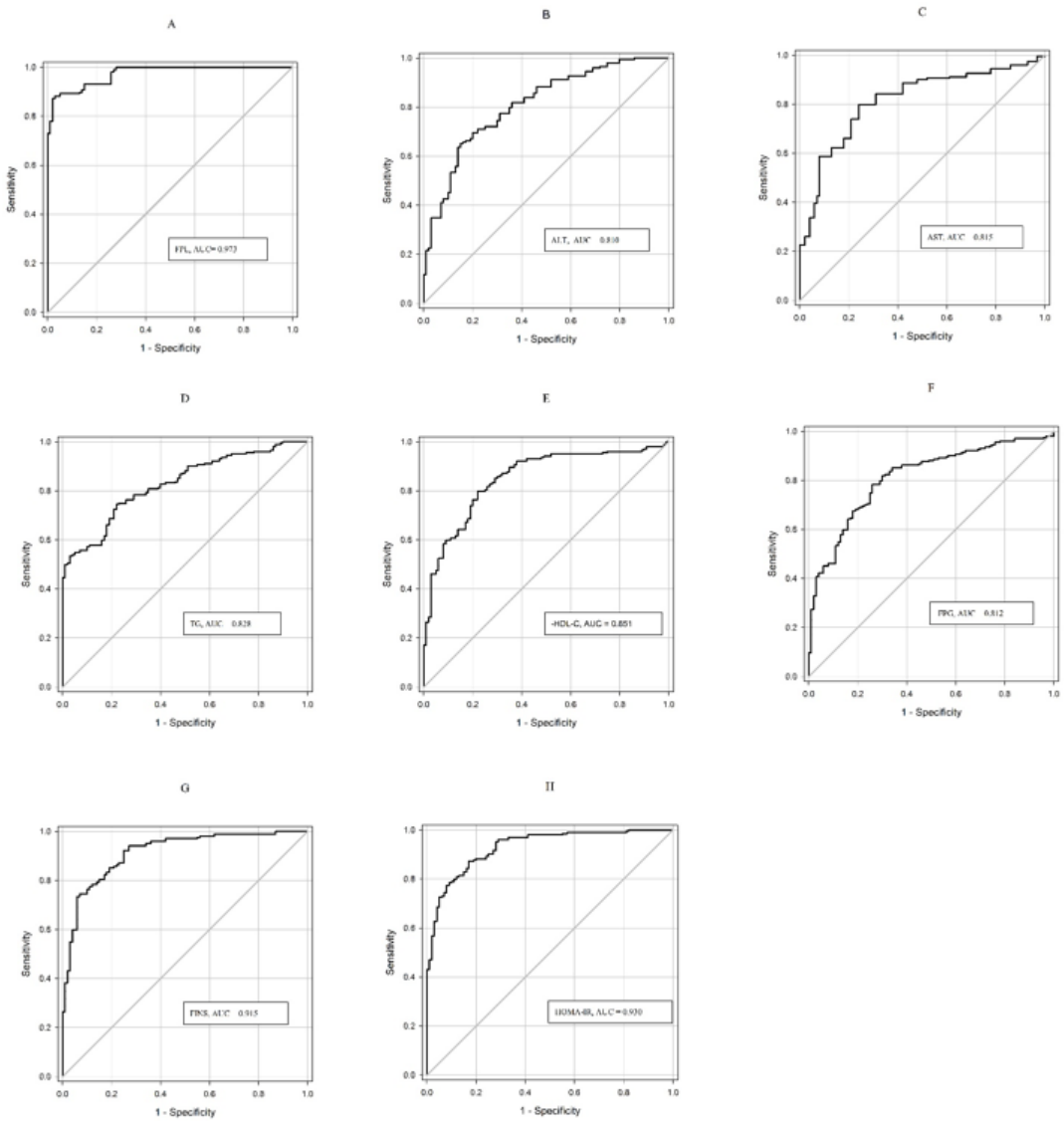

Figure 1

ROC curves of biochemical markers for diagnosing non-alcoholic fatty liver disease AUC: area under the curve; FPL: fasting plasma lactate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance

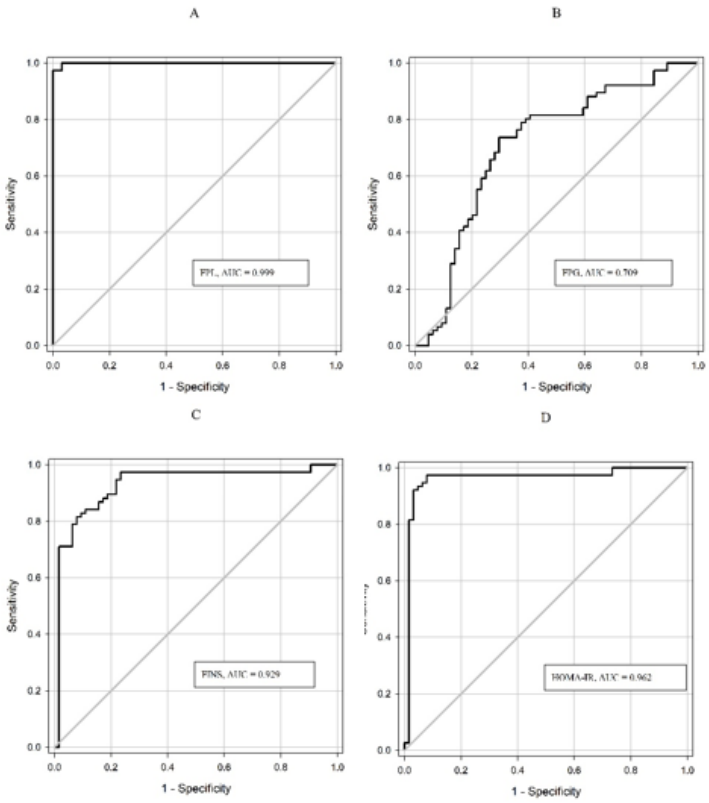

Figure 2

ROC curves of biochemical markers for staging non-alcoholic fatty liver disease AUC: area under the curve; FPL: fasting plasma lactate; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance.