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Original Article

Study on correlation between coagulation indexes and disease progression in patients with cirrhosis

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Abstract: Objective: To inquire into the significance of coagulation indexes in the progression of cirrhosis. Methods: A total of 108 patients with cirrhosis treated in our hospital were collected as the research group (RG), and 105 healthy people who underwent concurrent physical examination were selected as the control group (CG). The coagulation indexes of all the participants were tested to determine their significance in cirrhosis progression. Results: Compared with the CG, prothrombin time (PT), activated partial thrombin time (APTT) and thrombin time (TT) in the RG were statistically prolonged, while fibrinogen (FIB) was notably decreased (P<0.05). With the increase of Child-Pugh score, PT, APTT and TT prolonged and FIB reduced gradually (P<0.05). The coagulation indexes of patients were correlated with Child-Pugh score (P<0.05). Patients in the RG showed markedly higher alanine aminotransferase (ALT), total bilirubin (TBil), total bile acid (TBA), mean platelet volume (MPV), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR), with notably lower albumin (ALB), prealbumin (PA), platelet count (PLT) and coagulation factors compared with the CG. As the Child-Pugh score increased, the ALT, TBil, TBA, MPV, PDW and P-LCR gradually elevated in the RG (P<0.05), whilst coagulation factors, ALB, PLT and PA all gradually decreased (P<0.05). The value of area under the curve (AUC) of each coagulation index for early diagnosis of cirrhosis was >0.80, and the sensitivity was >80% (P<0.05). Conclusion: Coagulation indexes, coagulation factors, platelet parameters and liver function all effectively reflect the level of liver injury; especially which, coagulation indexes are related to the severity of liver injury, and can provide evidence for the early diagnosis of cirrhosis patients, with clinical significance.

Keywords: Coagulation indexes, cirrhosis, coagulation factors, platelet parameters, liver function

Introduction

Cirrhosis is one of the primary causes of death worldwide [1], which may be triggered by a combination of genetic and environmental factors [2]. Liver fibrosis can be induced by various liver diseases, including hepatitis, alcoholic liver injury and autoimmune liver disease [3]. It is also a major health problem as all chronic liver diseases will eventually lead to cirrhosis [4]. Studies have shown that the survival rate of liver cirrhosis is low, and the mortality rate is higher than that of the other five major cancers, i.e. lung cancer, colorectal cancer, stomach cancer, liver cancer and breast cancer [5]. Liver cancer ranks among the top five in morbidity and mortality all around the world, and in the development of liver cancer, fibrosis is often part of the repair process of liver injury, leading to cirrhosis [6].

Patients with cirrhosis are often accompanied by coagulation and hemostasis disorders [7], and are also more susceptible to life-threatening bacterial infections, resulting in a high incidence rate [8]. At present, the treatment of cirrhosis tends to be standardized, that is, reducing hepatic stellate cell activation, inhibiting fibrosis, increasing the degradation of matrix components, and decreasing activated myofibroblasts [9, 10]. However, as liver function is in the compensatory stages, neither liver function nor the functional reserve can reflect the pathological severity of cirrhosis [11]. The liver not only has functions of detoxification and inactivation, anabolism and bile excretion [12], but also it is the main organ in the body for the synthesis and inactivation of various coagulation factors, prothrombin and antithrombin [13]; which are essential in maintaining the balance between the coagulation system and the anticoagulation system [14].

Therefore, by comparing the coagulation indexes of participants in the two groups, this study mainly explored their significance in the progression of cirrhosis.

Information and methods

General information

Consisting of 64 males and 44 females, with an average age of (50.24±5.33) years, 108 cirrhosis patients who came to our hospital were enrolled in the RG. In addition, 105 healthy controls who underwent concurrent physical examination were collected as the CG, including 65 males and 40 females, with an average age of (51.01±5.27) years.

Inclusion criteria: Patients accompanied by family members at the time of admission, and was diagnosed with cirrhosis by biochemical [15] and imaging examination, with complete clinical data. Exclusion criteria: Patients with a history of drug dependence, a history of taking clotting drugs within the past 6 months, a history of mental illness, autoimmune system deficiency, and inability to cooperate with treatment due to communication disorders. This experiment was conducted with the approval of the hospital ethics committee, and each patient agreed and signed a complete informed consent form.

Methods

Fasting venous blood (15 ml) was collected from both groups in the early morning, with 5 ml kept in 3 separate anticoagulant tubes. After 60 min of coagulation (20-25°C), centrifugation was performed at 1369.55 rpm at 4°C for 15 min (Sichuan Shuke Instrument Co., Ltd., TG 112). The isolated upper serum was then stored in a freezer at -70°C for centralized detection. One anticoagulant tube was tested by STA-R Evolution automatic hemagglutination instrument (Beijing Stago Diagnostic Products Trading Co., Ltd., 58151) and matching reagents to detect coagulation of four indices and the activity of coagulation factors in the two groups; another vial of blood was used to detect platelet parameters of both groups with an automatic blood cell counter (Beijing Dakewe Biotechnology Co., Ltd., Cellometer AUTO T4), and the third vial was used to detect liver function with an automatic biochemical analyzer (Cisco North Biotechnology (Beijing) Co., Ltd., Catalyst One).

Outcome measures

Four coagulation indices were detected in the two groups. The classification (subgroups A, B and C) of patients in the RG was made by referring to the Child-Pugh score [16], with 5-6 points in subgroup A, 7-9 points in subgroup B and 10-15 points in subgroup C. Coagulation of the four indices in the three subgroups were observed and the correlation between coagulation indexes and child-Pugh scores in the RG was analyzed. Liver function parameters, platelet parameters and coagulation factors were measured and compared between the CG and the three subgroups. The value of coagulation indexes in the diagnosis of cirrhosis in the RG and CG was examined separately.

Statistical methods

The statistical analysis and illustrations of data were performed by SPSS 20.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7 (San Diego Graphpad Software Co., Ltd.) respectively. The counting data was described by [n (%)], and compared using chi-square test between groups. The measurement data were recorded as (x±s), and compared by t test between groups. The correlation was analyzed by Spearman correlation coefficient, and the sensitivity and specificity of each index were evaluated by the receiver operating characteristic (ROC) curve. $P<0.05$ indicated a statistically significant.

Results

Comparison of general data

See **Table 1** for general data of patients. The average age, body mass index (BMI), average height, smoking history and other general clinical data of participants showed no significant differences ($P>0.05$).

Comparison of four coagulation indices between two groups

The four coagulation indices were compared between the two groups, as shown in **Figure 1**. Compared with the CG, the PT, APTT and TT in the RG were remarkably prolonged ($P<0.05$),

Table 1. Comparison of general data between the two groups (x±sd)/[n (%)]

	Research group (n=108)	Control group (n=105)	t/X^2	P
Average age (years old)	50.24±5.33	51.01±5.27	1.06	0.29
Gender			0.16	0.69
Male	64 (59.26)	65 (61.90)	-	-
Female	44 (40.74)	40 (38.10)	-	-
Body mass index (kg/m^2)	22.46±2.34	22.58±2.31	0.38	0.71
Average height (cm)	172.65±10.58	172.43±10.14	0.15	0.88
History of smoking			0.09	0.77
Yes	72 (66.67)	68 (64.76)	-	-
No	36 (33.33)	37 (35.24)	-	-
Place of residence			0.12	0.73
Urban	56 (51.85)	52 (49.52)	-	-
Rural	52 (48.15)	53 (50.48)	-	-
Posthepatitis cirrhosis	78 (72.22)	0 (0.00)	-	-
Alcoholic cirrhosis	17 (15.74)	0 (0.00)	-	-
Biliary cirrhosis	8 (7.41)	0 (0.00)	-	-
Unexplained cirrhosis	5 (4.63)	0 (0.00)	-	-
Group A	36 (33.33)	0 (0.00)	-	-
Group B	35 (32.41)	0 (0.00)	-	-
Group C	37 (34.26)	0 (0.00)	-	-

while fibrinogen (FIB) was significantly decreased (P<0.05).

Comparison of the four coagulation indices among the three subgroups

The four coagulation indices were compared among the three subgroups, as shown in **Figure 2**. As the Child-Pugh score increased, PT, APTT and TT prolonged and FIB decreased gradually in the three subgroups, with significant differences (P<0.05).

Correlation analysis of coagulation indexes and Child-Pugh scores of patients in the RG

The correlation analysis of coagulation indexes and Child-Pugh scores of patients in the RG are shown in **Figure 3**. PT, APTT and TT were positively and significantly related to the Child-Pugh score (r=0.84, 0.70, 0.69 respectively, P<0.05), while FIB was negatively and siginifcantly associated with the Child-Pugh score (r=-0.62, P<0.05).

Comparison of liver function indexes between the subgroups and the CG

Comparison of liver function indexes between subgroup patients and the CG is shown in **Figure 4**. Compared with the CG, ALT, TBil and TBA were remarkably elevated, while ALB and PA evidently decreased in the three subgroups. With the increase of the Child-Pugh score, ALT, TBil and TBA increased gradually, while ALB and PA decreased gradually, and there were statistical differences among the subgroups (P<0.05).

Comparison of platelet parameters between the subgroups of RG and the CG

The comparison of platelet parameters between the subgroups and the CG is shown in **Figure 5**. Compared with the CG, the PLT of the patients in the three subgroups reduced significantly (P<0.05), while on the contrary, the MPV, PDW, and P-LCR increased dramatically (P<0.05). PLT gradually decreased, MPV, PDW and P-LCR gradually increased along with the increase of Child-Pugh score, and there were marked differences among the three subgroups (P<0.05).

Comparison of coagulation factors between the subgroups of RG and the CG

See **Figure 6** for the comparison of coagulation factors between the subgroups and the CG. Coagulation factors II, V, VII and X were significantly lower in the three subgroups compared to the CG (P<0.05). As the Child-Pugh score increased, these coagulation factors reduced gradually, with statistical differences among the three subgroups (P<0.05).

Single detection of the value of coagulation indexes in the diagnosis of cirrhosis

The coagulation indexes (PT, APTT, FIB and TT) in the RG and CG were tested to determine their diagnostic value, sensitivity, specificity and AUC (**Table 2** and **Figure 7**).

Discussion

Liver fibrosis is a dynamic process caused by the irregularity between fiber formation and

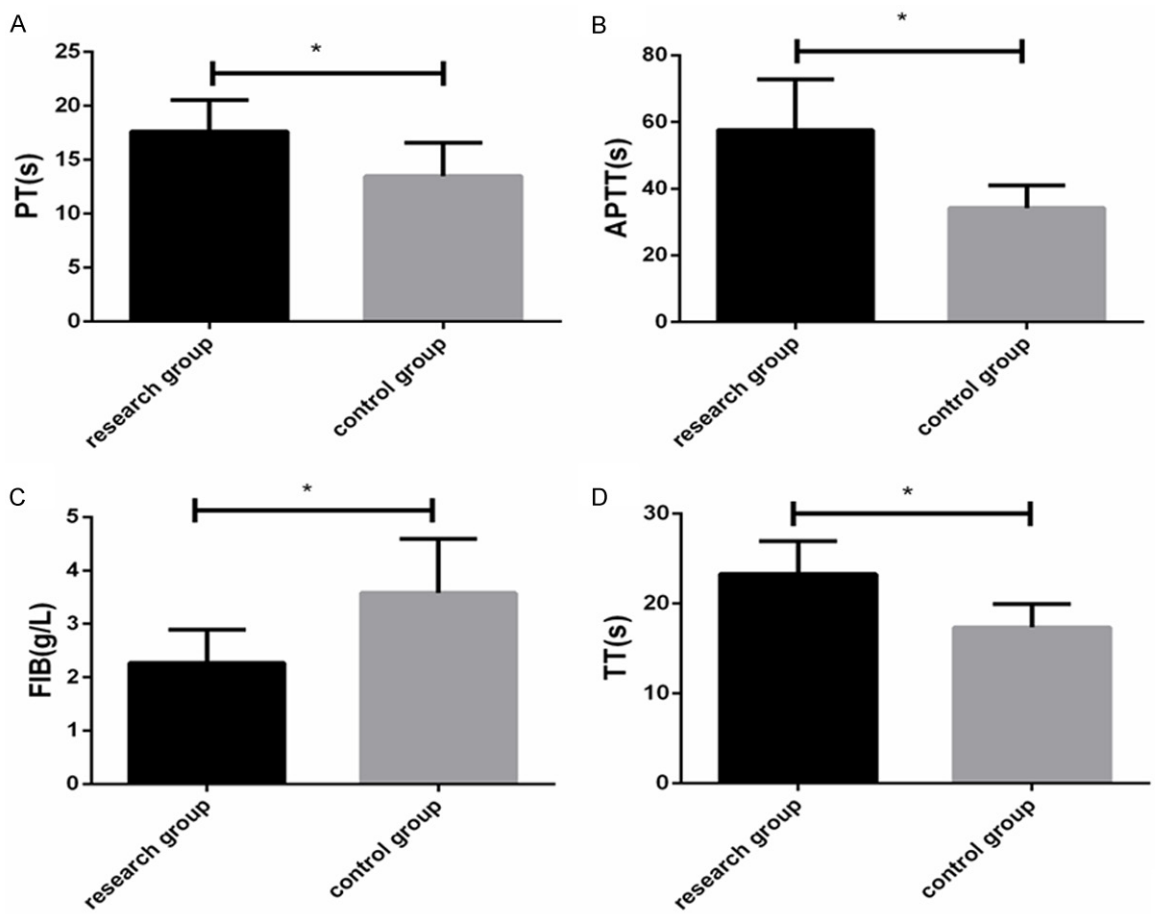

Figure 1. Comparison of four coagulation indices between two groups. A: PT in the research group was significantly longer than that in the control group; B: APTT was remarkably longer in the research group than in the control group; C: FIB was significanlty lower in the research group than in the control group; D: TT was evidently longer in the research group than in the control group. Note: * indicated P<0.05 compared between the two groups.

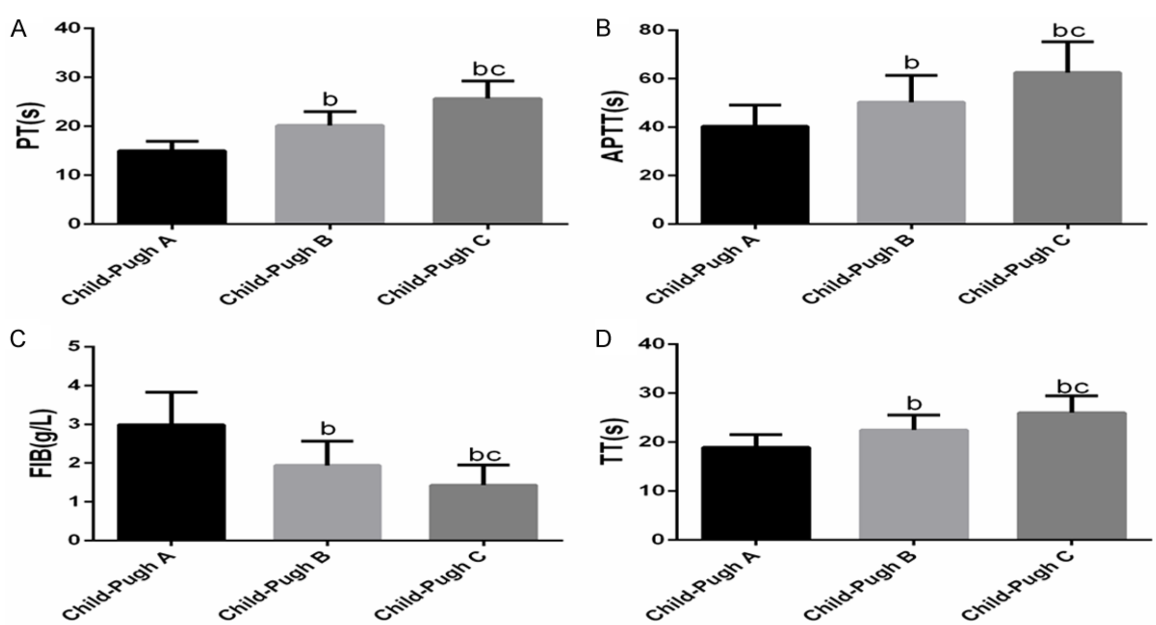

Figure 2. Comparison of four coagulation indices in three subgroups. A: PT became longer and longer as the Child-Pugh score increased; B: APTT became longer and longer as the Child-Pugh score increased; C: FIB became lower and lower as the Child-Pugh score increased; D: TT became longer and longer as the Child-Pugh score increased. Note: b indicated bP<0.05 compared with Child-Pugh group A; c indicated cP<0.05 compared with Child-Pugh group B.

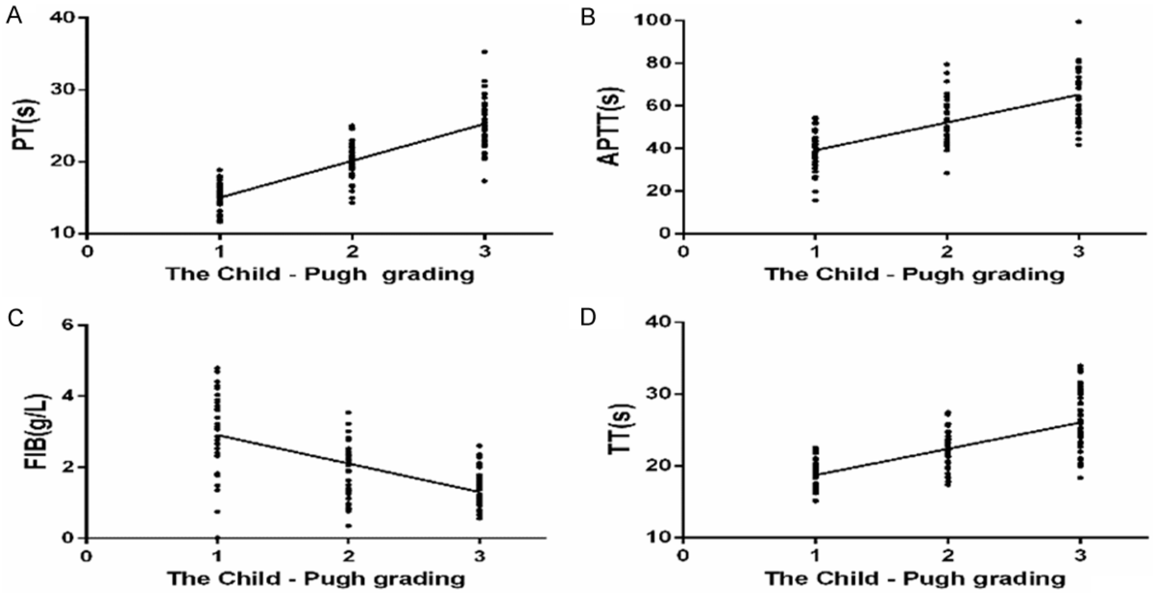

Figure 3. Correlation analysis of coagulation indexes and Child-Pugh scores. A, B, D: PT, APTT and TT were positively correlated with the Child-Pugh score; C: FIB and the Child-Pugh score were negatively correlated.

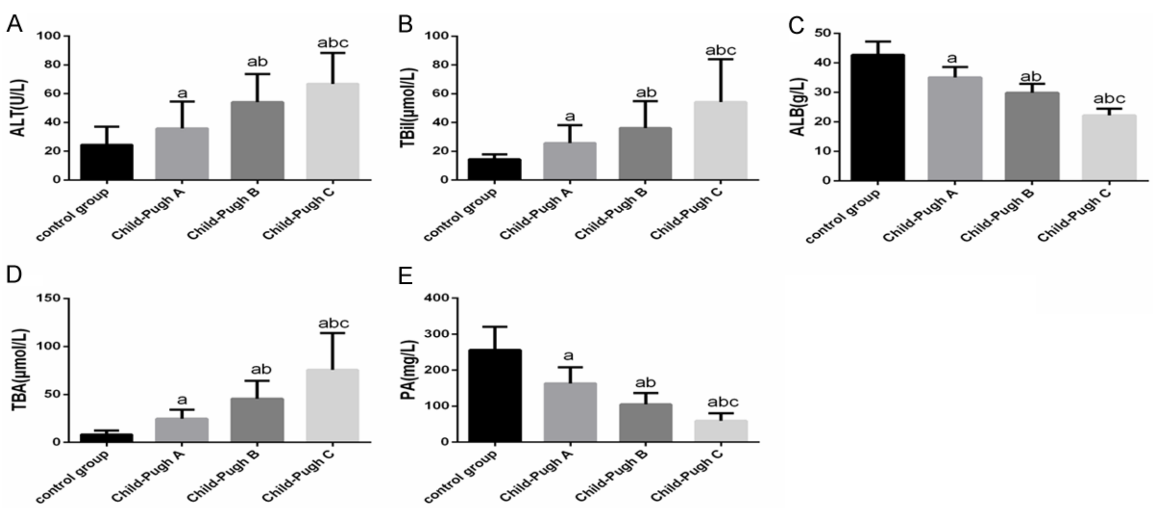

Figure 4. Comparison of liver function indexes between subgroups and control group. A, B, D: Compared with the control group, the ALT, TBil and TBA of the three subgroups increased significantly, and they increased gradually with the increase of Child-Pugh score; C, E: Compared with the control group, the ALB and PA decreased remarkably in the three subgroups, and they decreased gradually with the increase of Child-Pugh score. Note: a indicated aP<0.05 compared with the control group; b indicated bP<0.05 compared with Child-Pugh group A; c indicated cP<0.05 compared with Child-Pugh group B.

fibrinolysis, which can lead to cirrhosis over time [17]. In chronic liver disease, splenomegaly and hyper splenism will occur with the development of portal hypertension [18]. Being one

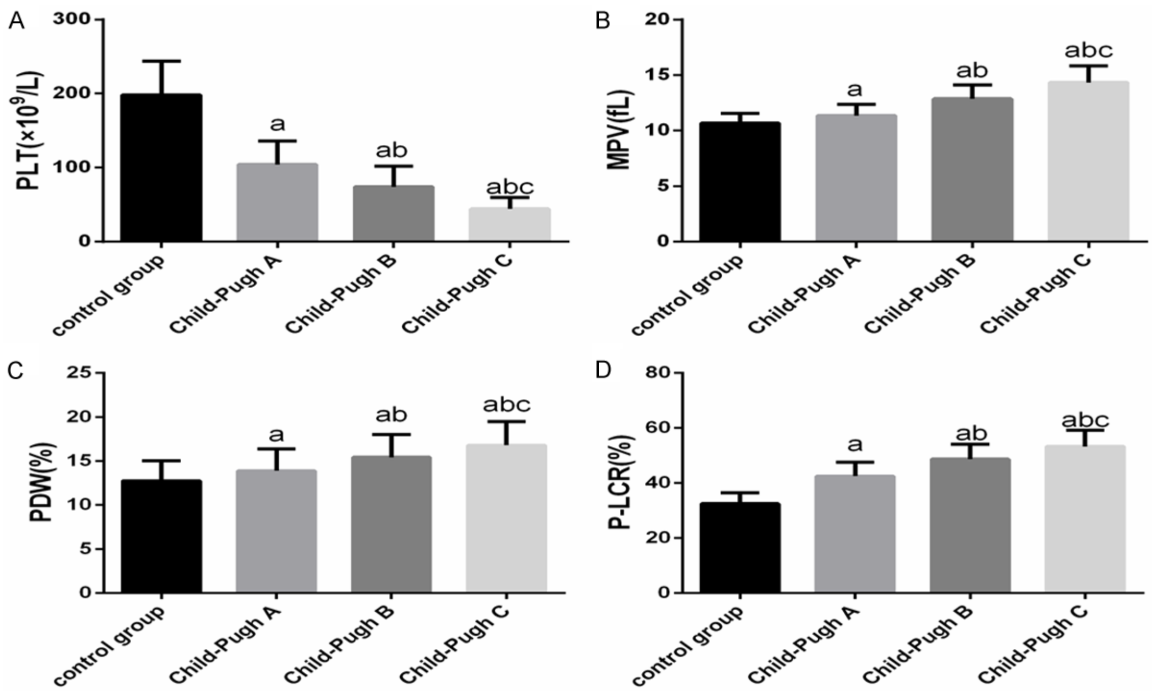

Figure 5. Comparison of platelet parameters between subgroups and control group. A: The PLT of the patients in the three subgroups decreased significantly compared with the control group, and it decreased with the increase of Child-Pugh score; B-D: Compared with the control group, the MPV, PDW, P-LCR of patients in the three subgroups increased significantly, and they increased gradually with the increase of Child-Pugh score. Note: a indicated a$P<0.05$ compared with the control group; b indicated b$P<0.05$ compared with Child-Pugh group A; c indicated c$P<0.05$ compared with Child-Pugh group B.

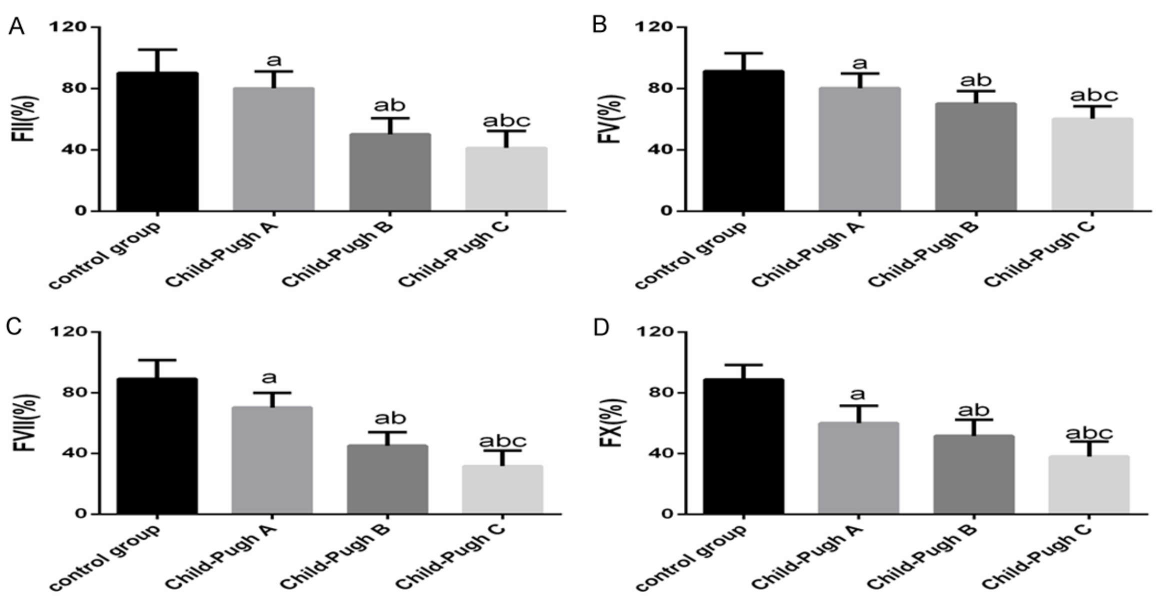

Figure 6. Comparison of coagulation factors between subgroups and control group. A: The coagulation factor II in the three subgroups decreased remarkably compared with the control group, and decreased gradually with the increase of Child-Pugh score; B: The coagulation factor V in the three subgroups decreased notably compared with the control group, and decreased gradually with the increase of Child-Pugh score; C: The coagulation factor VII in the three subgroups decreased dramatically compared with the control group, and decreased gradually with the increase of Child-Pugh score; D: The coagulation factor X in the three subgroups decreased statistically compared with the control group, and decreased gradually with the increase of Child-Pugh score. Note: a indicated a$P<0.05$ compared with the control group; b indicated b$P<0.05$ compared with Child-Pugh group A; c indicated c$P<0.05$ compared with Child-Pugh group B.

Table 2. Single detection of the value of coagulation indexes in the diagnosis of cirrhosis

	Specificity	Sensitivity	Optimal threshold	Youden index	AUC	P	95% confidence interval	
							Lower bound	Upper bound
PT	62.96%	90.48%	<17.91	0.03	0.85	0.00	0.80	0.90
APTT	71.30%	92.38%	<43.25	0.03	0.86	0.00	0.81	0.92
FIB	68.52%	86.67%	>2.49	0.03	0.82	0.00	0.77	0.88
TT	72.22%	86.67%	<19.88	0.03	0.84	0.00	0.79	0.90

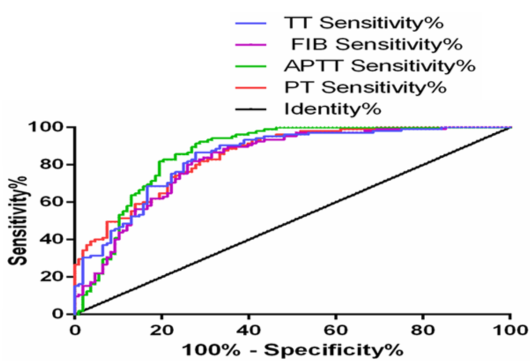

Figure 7. Area under the curve.

of the worst consequences of cirrhosis, portal hypertension is related to the formation of collateral vessels [19], and can also induce serious complications including hepatic encephalopathy [20]. At present, the Child-Pugh score is commonly used in clinical evaluation of the severity and prognosis of cirrhosis patients [21], but there are too many subjective and objective factors that can affect the grading, so it is paramount to search for early objective diagnosis indicators that can judge the severity of cirrhosis. Cirrhosis is characterized by liver fibrosis, hepatocyte damage, degeneration and necrosis, which leads to the synthesis of a series of coagulation factors, and the decreased ability of clearing thromboactive enzymes and activating fibrinolytic factor, resulting in the decrease of coagulation and anticoagulation function of the body. Therefore, theoretically, blood coagulation can reflect the severity of liver cirrhosis to a certain extent.

The coagulation function of the human body is the result of the coordination of platelets, coagulation system and coagulation factors [22]. In the present study, ALT, TBil and TBA were significantly higher while ALB and PA were significantly lower in the RG compared to CG. ALT has been proposed to be able to effectively reflect the damage of liver cells [23], and TBil and ALB are mainly indicators of liver fibrosis [24]. ALB and PA are synthesized by liver, of which PA has a half-life of only 1.9 days and is used to detect the liver's synthetic storage function, while TBA is used to detect the liver's synthetic and secretion function [25, 26]. They indicate that liver damage and abnormal liver function in patients with cirrhosis can be used as diagnostic indicators of cirrhosis. Further it was observed that, with the increase of Child-Pugh score, ALT, TBil and TBA increased gradually in the RG, while ALB and PA decreased gradually. In other words, the more serious the liver lesions were, the lower the liver function was, and the more abnormal the liver function indexes were, indicating that liver function can not only provide evidence for early diagnosis of cirrhosis, but also be an effective indicator to judge liver injury. For platelet detection, we used the indexes of PLT, MPV, PDW and P-LCR [27]. Compared with the CG, PLT was significantly lower in the RG, MPV, PDW and P-LCR were significantly higher, and platelet parameters in patients with liver cirrhosis were different from those in normal controls, demonstrating that platelet parameters can serve as indexes for the diagnosis of liver cirrhosis. Further detection identified that as Child-Pugh score increased, PLT gradually decreased, MPV, PDW and P-LCR gradually increased; that is, the more serious the liver lesions in patients with cirrhosis, the lower the platelet function, and the more abnormal the platelet parameters, indicating that the platelet parameters can effectively reflect the severity of liver lesions in patients with cirrhosis. Studies have shown that patients with liver damage may have dysregulation of coagulation and anticoagulation systems, as well as abnormal performance of coagulation indicators [28]. In this paper, the RG presented notably longer PT, APTT and TT, and significantly lower FIB than in the CG, which was in line with the preceding study. PT detects extrinsic coagulation pathway factors including the activity of coagulation factors II, V, and X [29]; APTT measures endogenous coagulation pathways factors including the activity of coagulation factors VIII, IX and XII [30]; TT records the time when fibrinogen is converted into fibrin [31]; and FIB is the fibrinogen synthesized by the liver [32]. Subsequently, it was identified that as the Child-Pugh score increased, PT, APTT and TT gradually extended and FIB gradually decreased, indicating that PT, APTT, FIB and TT were related to the severity of liver disease in patients with cirrhosis, and could be used as indicators to determine the severity of liver lesions in patients with cirrhosis. Moreover, coagulation factors II, V, VII and X were observed to be significantly lower in the RG than in the CG, and decreased gradually with the increase of Child-Pugh score, suggesting that coagulation factors II, V, VII and X were related to the severity of liver lesions in patients with liver cirrhosis and could be used as indicators for judging the severity of liver lesions in patients with liver cirrhosis.

Furthermore, the correlation between blood coagulation indexes and Child-Pugh scores in the RG was analyzed. It was found that the Child-Pugh score was positively correlated with PT, APTT and TT (r=0.84, 0.70, 0.69 respectively), and negatively correlated with FIB (r=0.62); further demonstrating that PT, APTT, FIB and TT can be indicators for liver lesion severity in patients with cirrhosis. Finally, we conducted detection on each index. The greater the AUC, the greater the diagnostic value. The AUC for the early diagnosis of cirrhosis by PT, APTT, FIB and TT was 0.85, 0.86, 0.82 and 0.84, respectively, and the sensitivity of all was above 80%, confirming that PT, APTT, FIB and TT may be indicators for early diagnosis of cirrhosis.

In this paper, the significance of coagulation indexes in the progression of liver cirrhosis was explored by detecting and recording four coagulation indices, coagulation factor activity, platelet parameters and liver function indexes of the two groups of participants, but there are still some certain limitations. For example, there is a lack of follow-up of patients in the design, and through the review of the literature, we can know that there is limited related literature about the combined detection of various indexes of blood coagulation. In the future, we hope to address the above shortcomings to obtain better experimental data and provide better theoretical support for clinical practice.

In summary, coagulation indexes, coagulation factors, platelet parameters and liver function all effectively reflect liver injury, among which coagulation indexes are related to the severity of liver injury and can provide a basis for the early diagnosis of patients with cirrhosis.

Disclosure of conflict of interest

None.

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