Combination With Glucocoriticoids and/or Immunosuppressants Brings Few Benefits in Patients With Primary Biliary Cholangitis

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Research Article

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Abstract

Objective To compare the efficacy of ursodeoxycholic acid (UDCA) monotherapy, and UDCA combined with glucocorticoids and/or immunosuppressants for patients with primary biliary cholangitis (PBC), and to search for relevant factors influencing the efficacy.

Methods This retrospective study enrolled 266 patients who were initially diagnosed with PBC were grouped according to different treatment regimes. We analyzed and compared demographic characteristics, immune parameters, biochemistry profiles and other indicators collected at baseline, six months and one year of treatment. The prognosis was evaluated by Paris II standard and GLOBE score. T test, chi-square test and logistic regression were used for statistical analysis.

Results According to Paris II standard and GLOBE score, there was no significant difference in one-year response rate and GLOBE score among the three treatment schemes ($P > 0.05$). GLOBE score > 0.3 indicated a decrease of the long-term survival rate, it was found that the long-term survival rate of the triple therapy group was significantly improved compared with the monotherapy group ($p=0.005$). Multivariate logistic regression analysis showed that PLT, ALP and ALB levels were risk factors for poor response. For the patients whose IgG levels were elevated but below twice upper limit of normal (ULN), the clinical benefit from combination therapy was not significant compared with monotherapy ($p>0.05$).

Conclusion: Compared with monotherapy, the double therapy did not improve the one-year efficacy and long-term survival rate of PBC patients. However, triple therapy may improve the long-term survival rate of patients, although it does not significantly improve the one-year efficacy.

Introduction

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease [1], with non-suppurative destruction of small bile ducts as the main pathological change. Without drug intervention, it may develop into hepatic fibrosis or even cirrhosis. The pathogenesis of PBC may be related to the loss of immune tolerance of mitochondrial antigens and subsequent humoral and cellular immunity, and environmental and genetic factors jointly promote the occurrence of the disease [2]. In the past, PBC was considered to be relatively rare. However, with the deepening understanding of the disease and the improvement of detection technology, the prevalence of PBC reported in the literature has been increasing year by year in recent years, ranging from 21.7 to 39.2 per 100,000 people from 2004 to 2014 [3].

Ursodeoxycholic acid (UDCA) is a first-line drug approved for the treatment of PBC, and its mechanism of action may be related to its cholagogic effect, stabilization of bile HCO_3^- protective umbrella, anti-apoptosis and endoplasmic reticulum stress [4]. In an international multicenter cohort study, the 10-year cumulative liver-free survival of patients treated with UDCA was significantly higher than that of untreated patients, and the benefits were significant regardless of gender, age, or disease stage [5]. Unfortunately,

about 40% of patients do not respond well to UDCA, and the liver transplant-free survival rate of these patients is significantly lower than in patients who respond well to UDCA[6].

Obeticholic acid (OCA) and Fibrates are considered as second-line drugs[7–9]. However, for patients with poor UDCA response, the combined treatment can significantly improve biochemical and itching symptoms, but large-scale population validation and evidence of long-term efficacy were still lacking.

The basic pathological change of PBC is non suppurative inflammation of small bile duct, accompanied with varying degrees of hepatocyte damage, which is manifested as interfacial hepatitis [10]. Ma Xiong et al found that 37.3% of the so-called pre PBC patients with positive anti-mitochondrial antibody (AMA) and normal ALP still had different degrees of interface hepatitis[11]. A retrospective study showed that the incidence of cirrhosis and complications, liver related death and liver transplantation rate in patients with PBC variant syndrome were significantly higher than those in patients with typical PBC [12]. Another retrospective study showed that the 5-year survival rate without adverse outcomes in PBC patients with autoimmune hepatitis (AIH) characteristics was significantly lower [13].

Glucocorticoids and immunosuppressants have shown certain efficacy in clinical practice, but due to the limited sample size and side effects, there is still a great controversy at present. For typical PBC, glucocorticoid therapy is not recommended, but for PBC-AIH overlap syndrome, it is recommended to combine glucocorticoid therapy with UDCA. In fact, more patients with some characteristics of AIH who do not meet the diagnostic criteria of overlap syndrome (OS) are clinically. In this study, we compared the therapeutic effects of UDCA alone, double therapy (UDCA combined with glucocorticoids or immunosuppressants) and triple therapy (UDCA combined with glucocorticoids and immunosuppressants) on PBC patients, and analyzed the influencing factors of treatment response, and looked for the characteristics of patients with poor response to UDCA, so as to lay a foundation for further finding the combined treatment scheme.

Material And Methods

Patient population

Between January 2013 to December 2018, a total of 3658 patients who were initially tested positive for AMA and/or AMA-M2 were collected from Peking University People's hospital information system. The criteria of AMA and / or AMA-M2 positive were AMA ≥ 1:40 (indirect immunofluorescence) and / or AMA-M2 (+) (Western blot) and / or AMA-M2 > 25ru / ml (ELISA).

Inclusion criteria: the diagnosis of PBC was based on the PBC guideline from 2018[14]; PBC was diagnosed, and treated with UDCA and other treatments in the hospital for the first time. Exclusion criteria: the diagnosis criteria were not met; PBC could not be diagnosed or the curative effect could not be determined due to the lack of clinical data; combined with other drugs, such as fibrates; the combined therapy time was less than 6 months. The study was carried out according to the guidelines of Helsinki

Declaration and was approved by the ethics committee of Peking University People's Hospital. All clinical data were collected after Peking University People's Hospital Ethics Review Committee approval (2019PHB279-01). All patients signed the informed consent form.

Data collection

The data as follows at baseline, half a year and one year after treatment were collected from the hospital information system: demographic characteristics: gender and age; immune parameters: IgA, IgG, IgM, AMA-M2; biochemistry profiles: ALT, AST, GGT, ALP, ALB, TBIL, PLT. In addition, the proportion of cirrhosis in the patients at baseline also recorded. Medical records of comorbidities were identified from hospital information system, it included conditions tested within 3 months prior to or after the first positive AMA and/or AMA-M2. The results of the tests were used to avoid the impact of data on the treatment. The comorbidities were classified according to the International Disease code (ICD-10).

Prognosis judgment

The Paris criteria and GLOBE score was used to evaluate the one-year efficacy and liver transplant-free survival. The data of each patients were obtained 1 year after the beginning of therapy.

The Paris criteria [15]: ALP and AST ≤ 1.5 upper limit of normal, with a normal bilirubin level.

The GLOBE score [16]: 0.044378 × age at start of UDCA therapy + 0.93982 × LN(bilirubin times the upper limit of normal [ULN] at 1 year follow-up) + 0.335648 × LN(alkaline phosphatase times the ULN at 1 year follow-up) − 2.266708 × albumin level times the lower limit of normal (LLN) at 1 year follow-up − 0.002581 × platelet count per 109/L at 1 year follow-up + 1.216865.

Statistical analysis

Demographics, baseline laboratory test results are reported descriptively using mean (SD) and median (IQR) values for continuous variables and numbers and percentages for categorical variables. Kolmogorov-Smirnov method was used to test the normality of measurement data. T test or one-way ANOVA method was used to compare samples or multiple samples of normal distribution data, If the variance is uneven, Welch variance analysis method is adopted. Two rates or two constituent ratios were compared by Chi-square test. Logistic regression model was used to analyze the risk factors and odds ratio (OR) associated with poor prognosis. All analyses were considered exploratory and were performed using SPSS 24.0 (IBM Corp.Armonk, NY, USA) and graphpad prism 7 (graphpad software, La Jolla, CA, USA), with $P < 0.05$ considered significant.

Results

Study population

Of the 3658 patients with positive AMA and /or AMA-M2 initially screened, 1825 patients did not meet the PBC diagnostic criteria, and 1036 patients could not be diagnosed due to serious lack of baseline data.

Among the other 797 patients who met PBC diagnostic criteria, 264 patients were excluded because UDCA medication records could not be found, and 162 patients were also excluded due to lack of follow-up examination. Among the remaining 371 patients, 35 patients were excluded due to taking other drugs, and 68 patients were excluded because they could not obtain complete clinical data for one year. In addition, 2 patients who had been treated with combination therapy for less than 6 months were excluded to reduce the possibility that the medication time was too short to work. Finally, 266 patients were included in the study, including 196 patients in the group A (UDCA monotherapy), 41 patients in the group B (UDCA combined with glucocorticoids or immunosuppressants), and 29 patients in the group C group (UDCA combined with glucocorticoids and immunosuppressants). (Fig. 1). The drug use of group B and group C was analyzed, prednisone and methylprednisolone were the main glucocorticoids, while cyclosporine, azathioprine and mycophenolate mofetil dispersible tablets were the main immunosuppressants.

Baseline Characteristics

The baseline demographics and clinical features of the enrolled patients are shown in Table 1. Of the 266 enrolled patients who were initially diagnosed with PBC, including 233 (87.6%) female and 33 (12.4%) male patients. These 266 patients were divided into three groups (group A, B and C) based on their therapy. Group A was treated with UDCA only, group B was treated with double therapy, and group C was treated with triple therapy, as shown above. The average age was 58.35 ± 11.02 years old. Compared with each other, there were no statistically significant differences in demographic, immunological indexes such as IgA, IgG, IgM, AMA-M2, biochemical indexes such as ALT, AST, GGT, ALP, ALB, TBIL, PLT and the proportion of baseline cirrhosis between the three groups ($P > 0.05$).

Table 1

Baseline Characteristics of PBC Patients. P value represents comparison between three groups. IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; AMA-M2: anti-mitochondrial antibody-M2; ALT: alanine amino-transferase; AST: aspartate aminotransferase; GGT: γ-glutamyl transpeptidase; ALP: alkaline phosphatase; ALB: albumin; TBIL: total bilirubin; PLT: platelets.

	All patients (n = 266)	Group A (n = 196)	Group B (n = 41)	Group C (n = 29)	P value
demographic characteristics					
Age	58.35 ± 11.02	58.95 ± 11.19	58.78 ± 10.72	53.83 + 9.46	0.058
Sex					
Female	233(87.6%)	170(86.7%)	37(90.2%)	26(89.6%)	0.758
Male	33(12.4%)	26(13.3%)	4(9.8%)	3(10.4%)	
immune parameters					
IgA G/L	3.14(0.35–20.30)	3.10(0.35–20.3)	3.46(0.82–16.70)	3.36(1.03–9.66)	0.986
IgG G/L	16.50(1.87–61.10)	16.40(1.87–61.1)	15.55(2.12–26.10)	18.90(2.92–46.10)	0.232
IgM G/L	2.90(0.456–30.30)	2.92(0.45–30.30)	2.99(0.83–10.50)	2.82(0.65–6.96)	0.879
AMA-M2	601.82(34.13-1033.36)	520.32(34.13-1033.36)	644.39(45.61-934.07)	658.89(514.19-803.59)	
biochemistry profiles					
ALT U/L	38(8-2010)	40.5(8-2010)	45(16–590)	28(13–784)	0.883
AST U/L	43(15-1370)	43(16-1370)	51(19–198)	36.5(15–544)	0.691
GGT U/L	129(8-1889)	130.5(8-1889)	129(16-1000)	106(25–472)	0.736
ALP U/L	142(43-1496)	139.5(43-1496)	185(58–908)	147(48–615)	0.216
ALB g/L	42.30(24.90–53.30)	42.55(24.90–53.30)	41.90(25.60–48.50)	42.20(30.70–50.40)	0.731
TBIL	15.00(4.70-150.10)	14.90(6.00-138.70)	14.80(7.90-150.10)	18.00(4.70–49.80)	0.080
PLT 10^9/L	183(6-502)	183(14–502)	181(11–327)	183(6-370)	0.646
liver cirrhosis	35(13.16%)	23(11.73%)	4(9.76%)	8(27.59%)	0.140

Age is expressed as mean ± SD. Other characteristics are shown as the median (minimum and maximum).

Treatment efficacy determined on the basis of the Paris standard

The response rates were 69.92%, 71.43%, 73.17% and 55.17% in total and Group A, B and C, respectively according to the Paris II standard. There was no significant difference in one-year response rate between the two groups (P > 0.05)(Table 2). Based on the three parameters of Paris II standard, the constituent ratio of non-responsive patients was compared, and it was found that there was no significant difference in the composition of the three groups (P > 0.05) (Table 3). This observation showed that there was no significant difference in one-year response rate among the three groups.

Table 2

The response of patients was compared based on Paris II standard. According to Chi square test, there was no significant difference in response rate between combination therapy and UDCA monotherapy.

	Response well	Response poor	P value
Group A (n = 196)	140	56	
Group B (n = 41)	30	11	0.822
Group C (n = 29)	16	13	0.081

Table 3

Patients with poor response meet the standard composition. Patients with poor response may be a single indicator, or two or even three indicators may not meet the response criteria. According to the statistics of this part of the population, there is no difference in the constituent ratio of patients with poor response.

	One indicator	Two indicators	Three indicators	P value
Group A	31	15	10	
Group B	4	4	3	0.631
Group C	8	2	3	

Calculation of the GLOBE Score

The GLOBE score of the three groups was calculated as shown in Fig. 2A. The scores of Group A, B and C were 0.82 ± 1.08, 0.68 ± 0.98, and 0.57 ± 1.06. Although we can see a more obvious downward trend, the difference was not statistically significant (P > 0.05). GLOBE score greater than 0.3 indicates a significant reduction in long-term survival compared with that of a matched general population [16]. The three groups were divided into two parts according to the GLOBE score of 0.3. It can be observed that the proportion of people with GLOBE score > 0.3 in the triple therapy group was significantly reduced (Fig. 2B and 2C). Chi-square test was carried out between the group B, C and the group A. The results showed that there were significant statistical differences between group C and group A (P = 0.005), while there were no statistical differences between group B and group A (p = 0.719) (Table 4). This observation suggests that PBC patients treated with triple therapy may have a higher long-term survival rate than UDCA monotherapy alone.

Table 4
Comparison of long-term survival rate of different treatment groups. According to the global score greater than 0.3, the number of patients in group C was significantly reduced.

	GLOBE score ≤ 0.3	GLOBE score > 0.3	P value
Group A (n = 196)	63	133	
Group B (n = 41)	12	29	0.719
Group C (n = 29)	17	12	0.005

Response of PBC patients with high IgG characteristics to combination therapy

Among 79 patients with higher IgG levels than normal, 74 patients were more than 1 ULN, and 5 cases were more than 2 ULN. According to the Paris II standard, the one-year response rate of PBC patients with high IgG characteristics was estimated. Compared with the group A, the clinical benefit of UDCA combined with glucocorticoids and /or immunosuppressants was not obvious compared with UDCA monotherapy (P > 0.05) (Table 5). By Welch analysis of variance, there was no significant difference in GLOBE score among patients with higher IgG levels of the three groups.

Table 5

Response ratios of patients with high IgG in different treatment groups. There was no significant difference in response rate between group B and group C with high IgG compared with group A.

Hjgh levels of IgG	Response well	Response poor	P value
Group A (n = 55)	29	26	
Group B (n = 12)	8	4	0.379
Group B (n = 12)	7	5	0.724

Univariate and multivariate analysis of patient response to treatment

Among 266 PBC patients, 186 (69.9%) responded well and 80 (30.1%) responded poorly. Univariate analysis showed that compared with patients with good response, the patients with poor response have higher proportion of male, higher levels of IgG, GGT, ALP and TBIL ($P < 0.05$), and lower levels of platelet count and ALB ($P < 0.05$). In multivariable logistic regression analysis, the statistically significant indicators were included. The results showed that higher ALP (OR = 1.010; $P < 0.001$; 95% CI: 1.005–1.015), lower PLT (OR = 0.992; $p = 0.009$; 95% CI: 0.987–0.998) and ALB levels (OR = 0.846; $P < 0.001$; 95% CI: 0.774–0.924) were associated with poor response (Table 6).

Table 6
Univariate and multivariate analysis of treatment response in all patients. OR = odds ratio.

	Univariable OR		Multivariable OR	
	OR(95% CI)	P value	OR(95% CI)	P value
Group		P = 0.123		
demographic characteristics				
Age		P = 0.851		
Sex				
Female	0.005(0.165–0.731)	P = 0.005		P = 0.099
Male				
PLT 10^9/L	0.993(0.989–0.997)	P < 0.001	0.992(0.987–0.998)	P = 0.009
Immunological indicators				
IgA G/L		P = 0.194		
IgG G/L	1.055(1.012-1.100)	P = 0.013		P = 0.387
IgM G/L		P = 0.987		
IgG:IgM		P = 0.978		
biochemical indicators				
ALT U/L		P = 0.757		
AST U/L		P = 0.399		
GGT U/L	1.003(1.002–1.006)	P < 0.001		P = 0.349
ALP U/L	1.010(1.007–1.013)	P < 0.001	1.010(1.005–1.015)	P < 0.001
ALB g/L	0.841(0.797–0.887)	P < 0.001	0.846(0.774–0.924)	P < 0.001
TBIL	1.039(1.021–1.057)	P < 0.001		P = 0.573

Discussion

As an autoimmune disease, people naturally think that glucocorticoid and /or immunosuppressants may have therapeutic effort on PBC. In the previous studies of UDCA combined with glucocorticoid or immunosuppressant[17,18], part of studies may indicate that it is effective, but limited by the sample size, observation time and population. different results also contradict each other, and most of the literatures were published a long time ago. Therefore, we conducted this retrospective study in PBC patients receiving UDCA monotherapy and combination therapy.

To carry out our study, it is necessary to estimate the outcome of treated patients. We used different models to predict the prognosis as accurately as possible. According to Paris II standard, patients after UDCA treatment for one year were judged by ALP, AST and bilirubin levels, which were divided into two groups: good response group and poor response group, but there was a defect that the prognosis of each patient could not be predicted [15]. Therefore, we used the GLOBE score system to collect indicators after UDCA treatment for one year to estimate the survival time without liver transplantation [16]. The clinical value of this score in Chinese patients also has been verified [19].

In the present study, although the main biochemical indicators such as ALT, AST, GGT in the combination therapy group show a downward trend than UDCA monotherapy group there is no significant difference in the one-year response rate between the three groups based on the Paris II standard, suggesting that the addition of glucocorticoids and/or immunosuppressants to UDCA cannot significantly improve the one-year efficacy. The long-term survival rate of patients was judged based on GLOBE score, GLOBE score > 0.3 means that the long-term survival rate is lower than the matched general population [16]. The study found that although there was no significant difference between combined therapy and UDCA monotherapy, triple therapy may improve the long-term survival rate of patients.

Glucocorticoids are widely used in inflammatory diseases, and their biological effects are mediated by glucocorticoid receptors antagonizing proinflammatory transcription factors [20]. In recent years, it has been suggested that glucocorticoids are effective in the treatment of cholestatic liver diseases, which may be related to the inhibition of bile acid synthesis and the promotion of bile acid reabsorption. Additionally, researchers have found that glucocorticoids can inhibit the production of bile acids by inhibiting the expression of CYP7A1, the rate limiting enzyme of bile acid synthesis [21], and can increase the top dependency bile acid sodium transporters (Asbt) expression to stimulate the absorption of bile acid and liver cells in the ileal the basolateral bile transporter (Ntcp) expression to increase liver bile acid intake [21,22]. Immunosuppressants are commonly used in the treatment of autoimmune diseases. Different drugs play different roles to regulate the immune response of the body. Generally speaking, on the one hand, it can reduce the number of lymphocytes by inhibiting the proliferation and activation of lymphocytes; on the other hand, it can inhibit the function of lymphocytes by inhibiting cytokines. Therefore, triple therapy may play a more effective role through different mechanisms of action between drugs.

Our study found that compared with monotherapy, triple therapy has few benefits for PBC patients in one year, but may improve the long-term survival rate of patients. For this seemingly contradictory conclusion, it may be caused by the disease characteristics of PBC itself. Although PBC is considered to be an autoimmune disease, it shows more damages related to free bile acid and secondary cholestasis. At present, some scholars believe that PBC is caused by the secretion defect of bicarbonate produced by biliary system[23]. In conclusion, immunosuppressive therapy has no effect or little effect on PBC, and there are adverse reactions. Therefore, the current guidelines do not recommend the use of immunosuppressive therapy [1]. Although there was no significant difference in IgG level among the three

groups, we can see that the median IgG level in group C (18.9) is higher than that in group A (16.40) and B (15.55), suggesting that the disease may continue to progress into variant syndrome, which may partly explain why the long-term survival rate of triple therapy will increase. In addition to the characteristics of pathogenesis, PBC is often associated with extrahepatic autoimmune diseases. Floreani made statistics on 361 cases of PBC patients during 1975–2012, and found that 221 patients (61.2%) had at least one kind of extrahepatic autoimmune disease [24], a study from China also showed that about half of the population with AMA positive had autoimmune diseases [25], but whether this is related to the increased long-term survival rate needs further study.

Some patients with PBC may overlap the characteristics of AIH, and there are two kinds of characteristics of autoimmune liver diseases at the same time, which is called overlap syndrome (OS). However, it is difficult to accurately judge and classify OS in clinical practice. Therefore, the International Autoimmune Hepatitis Group (IAIHG) recommends the use of variant syndrome to describe patients with two disease characteristics [26]. If PBC patients are accompanied with abnormal examination results, such as elevated IgG, it should be suspected whether there is variant syndrome [27]. According to Paris standard, IgG higher than 2 ULN is the diagnostic standard of variant syndrome [28]. The levels of IgG in 79 patients with high IgG were analyzed, there were 74 patients whose IgG level was higher than 1 ULN, and 5 patients were more than 2 ULN. Compared with UDCA monotherapy group, there was no significant difference in one-year efficacy of combination therapy for PBC patients with high IgG, suggesting that the clinical benefit of combined therapy is not obvious compared with UDCA monotherapy treatment. Although it is considered that variant syndrome is a potential population sensitive to immunosuppressive therapy, we should pay close attention to the IgG level of patients to prevent the over diagnosis of variant syndrome and avoid unnecessary immunosuppressive treatment. Since the number of cases greater than 2 ULN is too small, no statistical analysis was conducted.

Although UDCA combined with glucocorticoid or immunosuppressants may have few clinical benefits for PBC patients, other combined treatment options need to be considered for patients with poor clinical response to UDCA monotherapy. Therefore, early detection of patients with poor response to UDCA alone is an urgent problem to be solved in clinical practice. Previous studies have shown that age and gender [29], biochemical indicators [30] are the influencing factors of UDCA treatment response. According to Paris II standard, patients were divided into good response group and poor response group. Comparing the clinical data of the two groups at the beginning of treatment, it was found that compared to the good response group, the poor response group has higher percentage of male patients, the levels of IgG, GGT, ALP, TBIL at baseline were higher, and the levels of ALB and PLT were lower. Cholestasis is the key link in the pathogenesis of PBC, GGT and ALP are the enzyme markers of bile duct injury, and TBIL reflects the degree of cholestasis. The increase of the above indicators indicates that the degree of cholestasis is more serious, while the decrease of platelet and albumin levels can partly reflect the decline of liver function, which may explain the poor response results in mechanism. The above-mentioned risk factors and different treatment regimens were included in the multivariate logistic regression analysis. It was found that high ALP, low ALB and PLT were the risk factors affecting the response to treatment. Our

patients have no statistical difference in age, which is different from the previous study [30], which may be due to the young patients' neglect of disease symptoms leading to the bias of the included population and the small number of patients. Although the elevated level of IgG has not reached the diagnostic criteria of variant syndrome, this study still suggests that the elevated IgG level is related to poor response, and may be related to the characteristics of AIH, which needs further verification.

Our research has three main limitations. First of all, the number of patients treated with combination therapy was small. Only when patients go to other departments or have other diseases can they use glucocorticoid or immunosuppressants. Therefore, relatively few patients meet the inclusion criteria. At the beginning of the study, we further divided the double therapy group into UDCA combined with glucocorticoid or immunosuppressant group. However, there was no difference between the two groups in terms of baseline data and prognosis. Considering that the number of patients in the two groups was small, a comparison was made for the combination.

Secondly, we used the Paris II standard and GLOBE score to judge the prognosis of patients receiving combined treatment, which were only verified in PBC patients who received UDCA treatment for one year. However, the researchers found that the actual survival rate of UDCA combined with bezafibrate was higher than that estimated by GLOBE score [8]. Whether UDCA combined with glucocorticoid or immunosuppressive therapy also underestimated the survival rate needs further study.

Finally, the analysis was a retrospective study with a low level of evidence.

Conclusion

UDCA combined with glucocorticoids or immunosuppressants cannot improve the one-year efficacy and long-term survival rate of PBC patients compared with UDCA monotherapy. However, compared with UDCA alone, UDCA combined with glucocorticoids and immunosuppressants may improve the long-term survival rate of patients, although it does not significantly improve the one-year efficacy. UDCA combined with glucocorticoid or immunosuppressive agents cannot improve the response rate of patients with high IgG below twice the upper limit of normal value.

Declarations

Author contributions

B.F., Z.L.W, R.J., Y.D.X. and H.W. planned and designed the paper; R.J., Z.L.W. and M.H. collected the clinical data; Z.L.W and B.F. performed the data mining; Z.L.W and R.J. wrote the manuscript; B.F. revised the paper. All authors have reviewed and approved the final content.

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Disclosure of interest

The authors declare that they have no competing interest.

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Figures

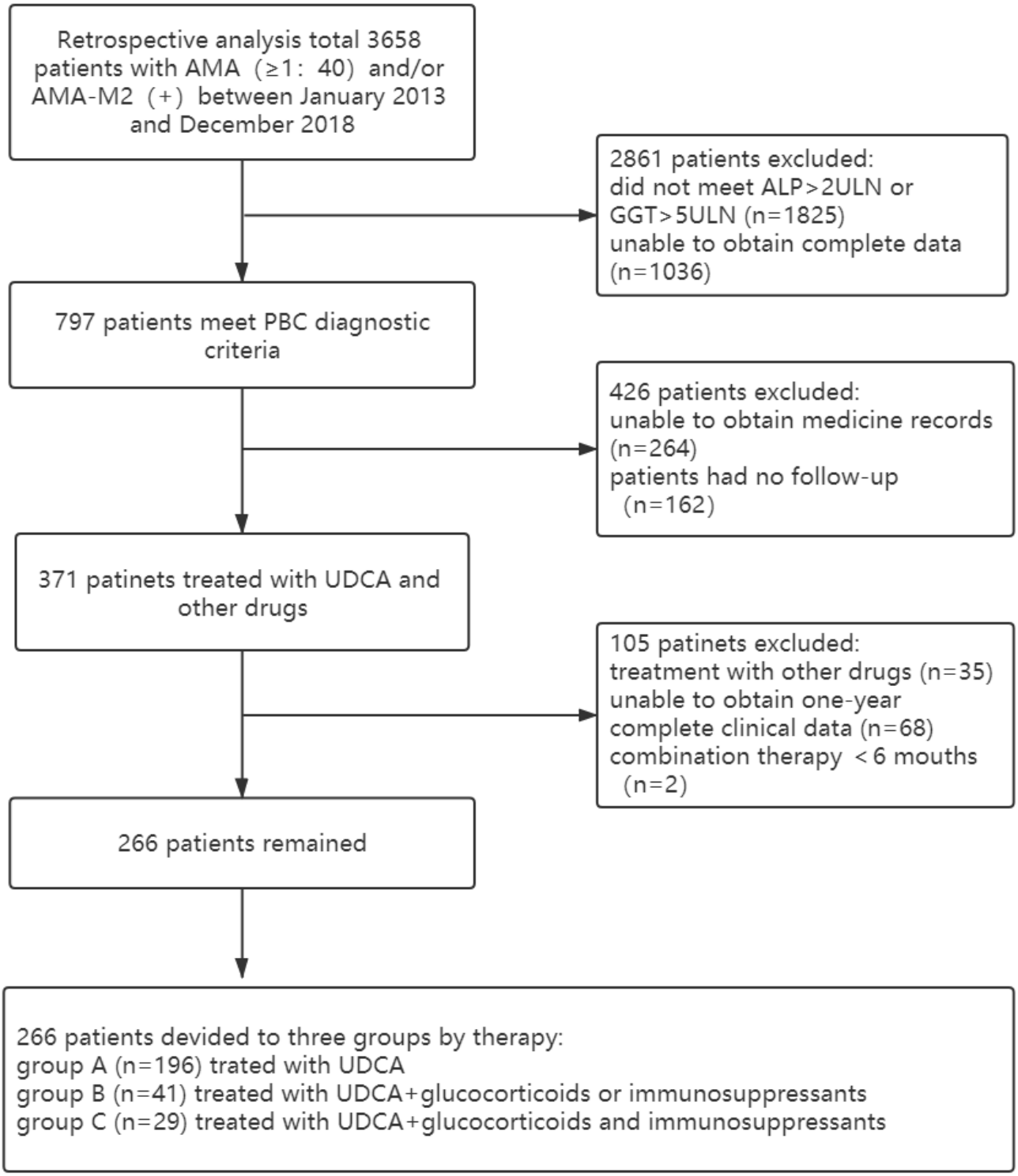

Figure 1

Flowchart of the patient selection process

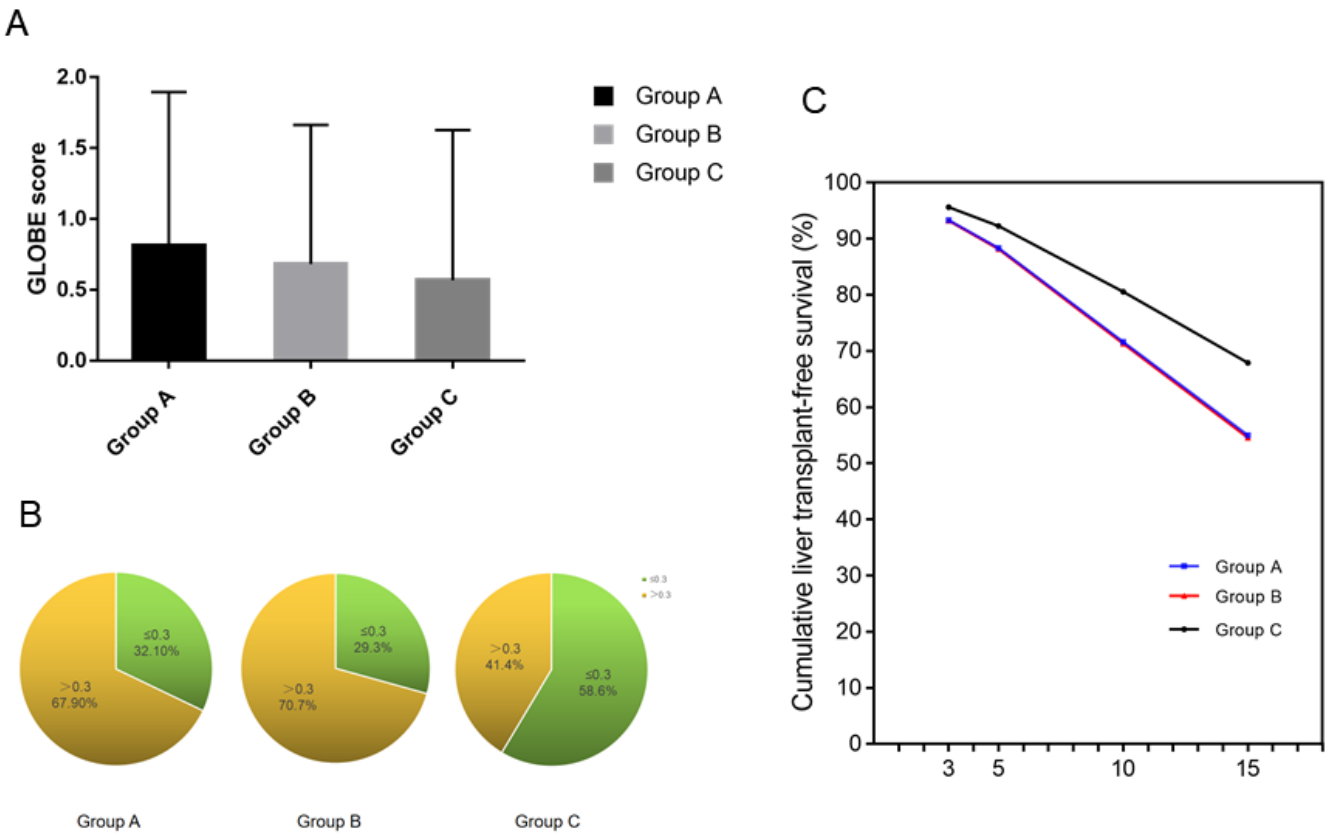

Figure 2

Survival analysis of different group. (A) The GLOBE score of three groups, data are expressed as the mean± SD. (B) Group with GLOBE score > 0.3, the proportion of three groups. (C) Transplant-free survival curves of different groups. Blue line show the group A, red line show group B and black line show group C.