Effectiveness of polyene phosphatidylcholine in metabolic-associated fatty liver disease treatment: A real-world study in China

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BACKGROUND AND RATIONALE

- While metabolic dysfunction-associated fatty liver disease (MASLD) has high global prevalence (32.4%),[1] it is also widely common in China (~30%)[2,3] and is frequently associated with metabolic diseases. It is estimated that the patient count for MAFLD will rise to approximately 314.58 million by the year 2030 in China.[4]
- Essential phospholipids (EPL) are a highly purified form of soybean-extracted polyenyl phosphatidylcholine (PPC) molecules and PPC are reported to be effective in patients with NAFLD associated with metabolic comorbidities.[5]
- PPC has a role in protecting liver function, stabilizing glucose control, and lowering blood lipids[6,7] and is recommended in Chinese MAFLD guidelines.[8]
- Therefore, facing with such a severe public health burden, there is a prime need for direct and strong evidence for the effectiveness of PPC in Chinese patients with MAFLD as a new concept in a real-world setting.

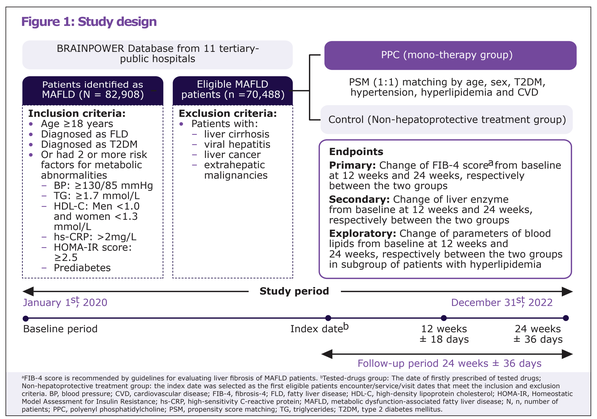
STUDY OBJECTIVE

- This retrospective observational study evaluates the effectiveness of PPC in delaying the course of liver fibrosis of patients with MAFLD in clinical practice in China.

METHODS

- Patients aged ≥18 with MAFLD were selected from 11 tertiary-public hospitals over the period from January 1, 2020, to December 31, 2022, in accordance with the Asian Pacific Association for the Study of the Liver (APASL) guidelines.[9]
- Patients were divided into two groups: PPC monotherapy group and control group (non-hepatoprotective treatment) and evaluated using propensity score matching (PSM).
- **Primary endpoint:** Changes of fibrosis-4 (FIB-4) index from baseline to 12 and 24 weeks between the two groups.
  Secondary endpoint: Changes in liver chemistries from baseline between the two groups at 12 and 24 weeks of the treatment.
  Exploratory endpoint: In MAFLD patients with hyperlipidemia, between-group differences in changes in blood lipids parameters were compared.
- Analysis of covariance (ANCOVA) was used to compare the within-individual changes of FIB-4 between treatment and control group.

Figure 1: Study design



[a]FIB-4 score is recommended by guidelines for evaluating liver fibrosis of MAFLD patients. [b]Tested-drugs group: The date of firstly prescribed of tested drugs; Non-hepatoprotective treatment group: the index date was selected as the first eligible patients encounter/service/visit dates that meet the inclusion and exclusion criteria. BP, blood pressure; CVD, cardiovascular disease; FIB-4, fibrosis-4; FLD, fatty liver disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; MAFLD, metabolic dysfunction-associated fatty liver disease; N, n, number of patients; PPC, polyenyl phosphatidylcholine; PSM, propensity score matching; TG, triglycerides; T2DM, type 2 diabetes mellitus.

RESULTS

Clinical characteristics of MAFLD patients

- In the database, 82,908 patients with MAFLD were identified, of which 53,282 (64.27%) were male. Patients with MAFLD were mostly from the age group of 50-59 years (29.35%).
- FIB-4 index, used to assess the amount of scarring, or fibrosis in the liver, showed a median value of 1.22 (interquartile range [IQR], 0.83–1.85) of total patients with MAFLD. Patients with intermediate-high risk, FIB-4 score were found to be 45.7% in the total population, and significantly higher in the diabetes and hypertension subgroups.
- Among the MAFLD cohort, 7093 (8.55%) patients were treated with PPC. Out of these patients around 68.25% were male. The highest PPC treatment rate was observed in patients belonging to 50-59 years age group (23.28%) (**Table 1**). Male patients were predominant in the 18-49 years age group, consistent with the general trend across all MAFLD patients.

RESULTS (Cont'd)

- Nearly, half of the patients treated with PPC exhibited abnormal aspartate transaminase (AST) levels, and 65.57% had abnormal alanine transaminase (ALT) levels.
- Based on the FIB-4-based fibrosis risk stratification, 47.6% were classified as intermediate and high risk.
- Nearly half (48.5%) of the MAFLD patients were found to have type 2 diabetes mellitus (T2DM) along with other comorbidities, such as cardiovascular diseases (CVD) (41.9%), hyperlipidemia (40.28%), and hypertension (38.64%) (**Table 1**) (**Figure 2**).

Table 1: Patient demographics and characteristics of MAFLD patients treated with PPC (N=7093)

Categories		Demographic characteristics	MAFLD patients treated with PPC
Demographic characteristics, n (%)	Age	<30 years	584 (8.23)
		30-39 years	1416 (19.96)
		40-49 years	1480 (20.87)
		50-59 years	1651 (23.28)
		60-69 years	1191 (16.79)
		≥70 years	771 (10.87)
	Sex	Female	2252 (31.75)
		Male	4841 (68.25)
Laboratory parameters, median (IQR)		**Liver Function Index**	
		AST (U/L)	39.00 (25.60-64.00)
		AST>40, n(%)	2196 (48.22%)
		ALT (U/L)	57.40 (30.60-97.65)
		ALT>40, n(%)	3037 (65.57%)
		TBiL (μmol/L)	13.70 (10.30–19.20
		ALP (U/L)	84.00 (68.00-107.00)
		GGT (U/L)	45.00 (41.30-48.00)
		FIB-4	1.24 (0.76-2.18)
		FIB-4 score ≥1.30	1712 (47.63%)
		Low risk (<1.30), n (%)	1882 (52.37%)
		Intermediate risk (1.3–2.67), n (%)	1034 (28.77%)
		High risk (>2.67), n (%)	678 (18.86%)
		Blood Glucose	
		FPG (mmol/L)	6.13 (5.32-8.07)
		HbA1c (%)	6.40 (5.80-7.70)
		Blood Lipid	
		HDL-C mmol/L)	1.02 (0.88-1.23)
		LDL-C (mmol/L)	3.00 (2.36-3.64)
		TC (mmol/L)	4.78 (4.01-5.61)
		TG (mmol/L)	2.13 (1.54-3.12)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; FIB-4, fibrosis-4; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; N, *n*, number of patients; PPC, polyenyl phosphatidylcholine; TBiL, total bilirubin; TC, total cholesterol; TG, triglycerides.

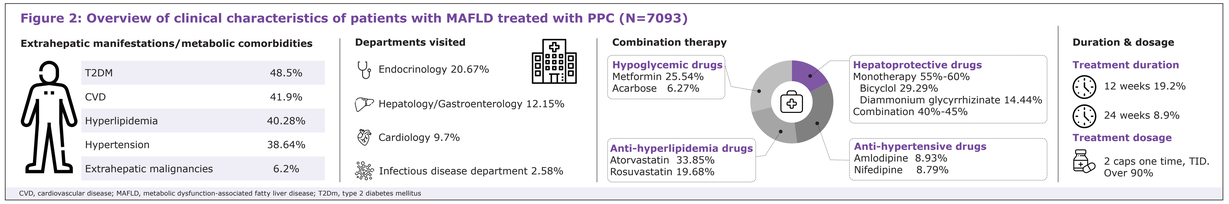
- Among the 7093 patients, most visited department was endocrinology (20.67%), followed by gastroenterology (12.15%), and cardiology (9.70%) (**Figure 2**).
- The primary hepatoprotective drug administered to patients along with PPC was bicyclol (29.29%), followed by diammonium glycyrrhizinate (14.44%), and compound glycyrrhizin (13.35%). The most common antidiabetic, antihypertensive, and lipid-lowering drugs used in combination with PPC were metformin (25.54%), amlodipine (8.93%) and atorvastatin (33.85%), respectively (**Figure 2**).

Table 2: Baseline characteristics before and after PSM (Fib-4, 24 weeks)

Baseline variables	Before PSM			After PSM		
	PPC group (n=42)	Control group (n=3117)	p-value	PPC group (n=42)	Control group (n=42)	p-value
Age (years), mean±SD	57.98±17.11	55.83±14.91	0.4242	57.98±17.11	57.00±16.79	0.7925
Sex, Male n (%)	25 (59.52)	1905 (61.12)	0.8740	25 (59.52)	25 (59.52)	1.0000
T2DM, n (%)	26 (61.9)	1669 (53.55)	0.3502	26 (61.90)	27 (64.29)	1.0000
Hypertension, n (%)	23 (54.76)	1772 (56.85)	0.8756	23 (54.76)	23 (54.76)	1.0000
Hyperlipidemia, n (%)	33 (78.57)	2722 (87.33)	0.1014	33 (78.57)	33 (78.57)	1.0000
CVD, n (%)	35 (83.33)	2384 (76.48)	0.3617	35 (83.33)	35 (83.33)	1.0000

CVD, cardiovascular disease; FIB-4, fibrosis-4; n, number of patients; PPC, polyenyl phosphatidylcholine; PSM, propensity score matching; SD, standard difference; T2DM, type 2 diabetes mellitus.

Figure 2: Overview of clinical characteristics of patients with MAFLD treated with PPC (N=7093)



CVD, cardiovascular disease; MAFLD, metabolic dysfunction-associated fatty liver disease; T2Dm, type 2 diabetes mellitus

Effects of PPC on liver fibrosis

- Data was available from 42 of 291 patients treated with PPC alone over 24 weeks, to evaluate the FIB-4 outcomes. For the control group, PSM was used to identify another 42 well-matched MAFLD patients who did not receive hepatoprotective therapy (**Table 2**).
- At 24-week, the changes of FIB-4 relative to baseline were significantly higher than in the control group of patients without hepatoprotective drugs (-0.12±0.62 for PPC vs. 0.11±0.50 for control, *P*=0.034) (**Figure 3**), indicating beneficial effects of PPC for fibrosis risk reduction. No significant difference between groups was observed when comparing the change of FIB-4 at 12 weeks.

Effects of PPC on liver enzymes

- The improvements of AST level from baseline to 12 weeks were significantly higher in the PPC group (-6.25±15.18 for PPC vs. -2.41±15.40 for control, *P*=0.0392) (**Figure 4**).
- PPC group showed a decreasing trend in ALT levels from baseline to 12 and 24 weeks vs control group, although this difference was not statistically significant.

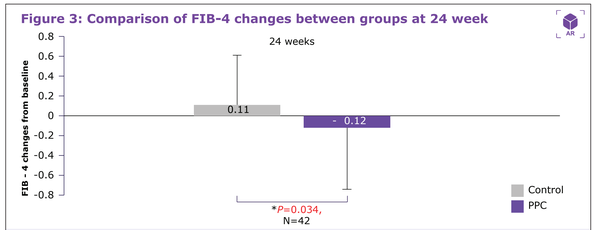
Effects of PPC on total bilirubin (TBiL) levels

- Significant reduction in TBiL levels from baseline were observed at both 12 and 24 weeks in the PPC group (12 weeks: -1.97±5.93 for PPC vs. 0.23±6.12 for control, *P*=0.0122; 24 weeks: -3.39±5.65 for PPC vs. 1.24±3.94 for control, *P*=0.0010) compared to control group (**Figure 5**).

Effects of PPC on low-density lipoprotein cholesterol (LDL-C) hyperlipidemia

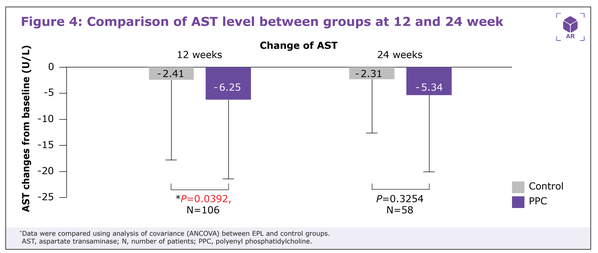
- During the 12 week treatment period, the PPC monotherapy group had a significantly larger reduction of LDL-C levels compared to control (12 weeks: -0.23±0.71 for PPC vs. 0.13±0.67 for control, *P*=0.0442; 24 weeks: -0.24±0.95 for PPC vs. -0.03±0.82 for control, *P*=0.4444) (**Figure 6**).
- In patients with hyperlipidemia, reduction in LDL-C levels indicates the positive effect of PPC in improving fibrosis in MAFLD patients.

Figure 3: Comparison of FIB-4 changes between groups at 24 week



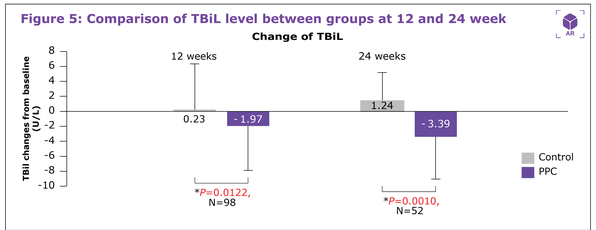
[1]Data were compared using analysis of covariance (ANCOVA) between EPL and control groups. FIB-4, fibrosis-4; N, number of patients; PPC, polyenyl phosphatidylcholine.

Figure 4: Comparison of AST level between groups at 12 and 24 week



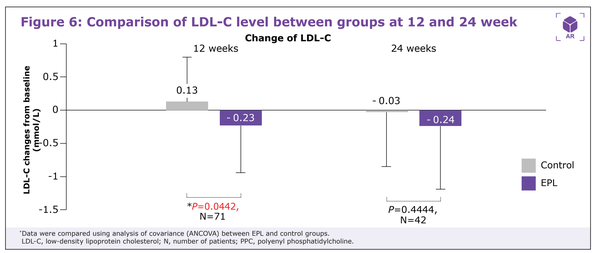
[1]Data were compared using analysis of covariance (ANCOVA) between EPL and control groups. AST, aspartate transaminase; N, number of patients; PPC, polyenyl phosphatidylcholine.

Figure 5: Comparison of TBiL level between groups at 12 and 24 week



[1]Data were compared using analysis of covariance (ANCOVA) between EPL and control groups. N, number of patients; TBiL, total bilirubin; PPC, polyenyl phosphatidylcholine.

Figure 6: Comparison of LDL-C level between groups at 12 and 24 week



[1]Data were compared using analysis of covariance (ANCOVA) between EPL and control groups. LDL-C, low-density lipoprotein cholesterol; N, number of patients; PPC, polyenyl phosphatidylcholine.

CONCLUSION

- Patients with MAFLD have a high burden of comorbidities such as CVD, T2DM, hypertension, etc. Nearly half (45.7%) of these patients have a medium-to-high risk of liver scarring, as shown by their FIB-4 index scores.
- Currently, there's a notable lack of effective management for MAFLD in China.
- The findings of this study in Chinese population indicate that PPC treatment can lower the risk of liver fibrosis, improve liver function and lipid profiles.
- PPC therapy is a viable option for patients with MAFLD with considerable liver inflammation (elevated ALT/AST) and those at risk of significant fibrosis, particularly in patients with T2DM and/or cardiovascular metabolic risk factors.

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CONFLICT OF INTEREST
The authors have no conflict of interest.

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