

Original Article

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Polyene phosphatidylcholine for liver function improvement in liver–injury patients: A multicenter retrospective study

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ABSTRACT

Objective: To investigate the heterogeneous effects of polyene phosphatidylcholine (PPC) on different liver diseases.**Methods:** This multicenter retrospective study used the Cooperative Registry of Hospital Prescription from 264 Grade-A hospitals in 16 provinces in China. Eligible patients had abnormal baseline liver functions and follow-up liver function tests. We used linear mixed-effects growth curve analysis to analyze the change of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and total bilirubin after adjusting for age and sex. Statistical significance was set at $P < 0.05$.**Results:** Among 1 454 patients (median age 52 years; 63.8% male), PPC significantly controlled abnormal ALT, AST, GGT and total bilirubin ($P < 0.05$). Patients with drug-induced liver injury exhibited higher baseline ALT levels and more rapid ALT decline. Cirrhotic patients had lower baseline ALT/AST and slower recovery. Patients with alcoholic liver disease had a sharp GGT decline ($P < 0.001$). ALT/AST recovery was not impacted by autoimmune hepatitis. Patients with higher baseline ALT received higher PPC doses, resulting in an adequate ALT/AST normalization time.**Conclusions:** PPC's hepatoprotective effects differed by liver disease subtypes. Higher doses suited patients with elevated baseline ALT/AST.**KEYWORDS:** Polyene phosphatidylcholine; Liver function; Liver injury; Liver disease

1. Introduction

Liver injury, which is common in the clinic, can be caused by

various factors, such as viral infection, drug abuse, and heavy alcohol consumption. When hepatocytes are injured, membrane permeability increases, and liver enzymes in the cytoplasm are released into the blood. Liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT), are often used as clinical markers to screen for liver diseases. Long-term liver injury can often lead to liver fibrosis and is an essential factor for the development of liver cirrhosis and hepatocellular carcinoma. Therefore, controlling

Summary

Question: What is the heterogeneous effect of polyene phosphatidylcholine (PPC) on different liver diseases?**Findings:** PPC treatment produced significantly more rapid declines in elevated alanine aminotransferase among drug-induced liver injury patients and gamma-glutamyl transpeptidase among patients with alcoholic liver disease, whereas normalization of alanine aminotransferase/aspartate aminotransferase was slower in cirrhotic patients.**Meaning:** Although PPC is effective for multiple liver disorders, patients with distinct hepatic conditions may derive differing degrees of therapeutic benefit.[#]These authors contributed equally to this work.[✉]To whom correspondence may be addressed. E-mail: yyy@bjmu.edu.cn; xiaoyuanxu6@163.com

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liver injury development holds great clinical significance for treating liver diseases.

Polyene phosphatidylcholine (PPC) is a major component of essential phospholipids. It is purified from soybean extract, has a high affinity for cellular membranes, and has demonstrated hepatoprotective effects in multiple *in vitro* or animal models[1]. PPC was found to suppress caspase-3 cleavage and phosphorylation of mixed lineage kinase domain-like protein in the livers of mice with induced lipid metabolic disorders, and to attenuate chromatin condensation and lipid droplet accumulation[2]. PPC has been used in China for years to lower abnormally increased liver enzyme levels[3–5]. Studies have evaluated the efficacy of PPC, either alone or in combination with other drugs such as glutathione or magnesium isoglycyrrhizinate, in different liver diseases, such as nonalcoholic liver disease[6,7], chemotherapy-induced hepatic injury[8], antituberculosis drug-induced liver injury[9], and liver cancer[4]. Researchers have reported that essential phospholipids, including PPC, exhibit antioxidant, anti-inflammatory and cellular membrane-protective effects[10,11]. In particular, PPC can downregulate reactive oxygen species-generating enzymes and inhibit apoptosis[12]. This may represent a unique mechanism accounting for the hepatoprotective effects of PPC. Although PPC is widely used in the management of patients with elevated liver enzymes, therapeutic efficacy is heterogeneous owing to diverse mechanisms of hepatocellular injury across different liver diseases. Elucidating these differential treatment responses is clinically important[13]. However, there is a lack of studies comparing the trajectories of liver-function across different liver diseases in real-world clinical settings.

Our previous real-world study demonstrated that PPC reduces ALT and AST levels in patients with hepatitis B virus (HBV) infection, with therapeutic efficacy comparable to that of conventional glutathione (GSH) and magnesium isoglycyrrhizinate therapies[14]. The aim of this secondary analysis was to further examine the heterogeneous efficacy of PPC and evaluate the effects of different doses by comparing the liver-function trajectories in different liver diseases during PPC treatment.

2. Methods

2.1. Study design

This was a multicenter, retrospective observational study featuring electronic medical data from the Cooperative Registry of Hospital

Prescription that included 264 Level-A hospitals in 16 provinces in China[15]. The data from patients hospitalized during October 2018 to September 2019 were used for this analysis. The research was approved by the Ethics Committee, and the requirement for obtaining informed consent from patients was exempted because of the retrospective design of the study (No. 2021-434).

2.2. Cohort selection

Patient selection is illustrated in Figure 1. Patients were included in the analysis cohort if they met the following criteria: had above normal level liver enzymes at baseline (defined according to Chinese standards in clinical practice: ALT >28 U/L for female and >40 U/L for male, or AST >40 U/L, or GGT >32 U/L for female and >50 U/L for male, or total bilirubin >17.1 $\mu\text{mol/L}$) and at least one follow-up liver function test since onset of PPC treatment (day 1 to day 14) were included in the analysis cohort. Patients with HBV infection and concomitant therapy with other hepatoprotective drugs were excluded. Finally, individuals who were diagnosed with hepatitis A virus (HAV) infection, hepatitis C virus (HCV) infection, autoimmune hepatitis (AIH), alcoholic liver disease (ALD), nonalcoholic steatohepatitis (NASH), drug-induced liver injury (DILI), cirrhosis, hepatocellular carcinoma (HCC), or non-liver cancer were included in the cohort.

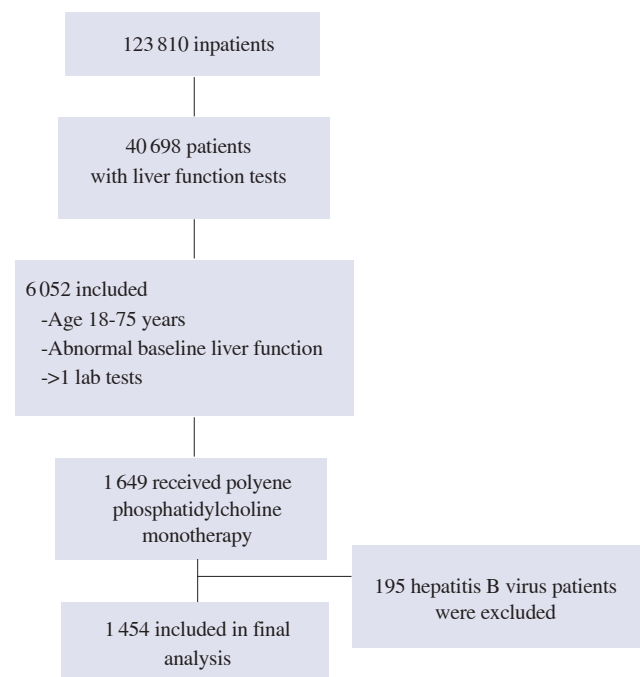


Figure 1. Flow chart of patient selection.

The diagnosis of liver diseases followed Chinese standards for diagnosis and treatment of liver disease and was recorded in the

registry based on discharge records. Patients may have multiple diagnoses and be included in more than one subgroup. PPC extract was administered *via* intravenous injection, with each vial containing 232.5 mg. A range of 1 to 8 vials were administered per injection, including 15 patients who received 1 vial, 653 received 2 vials, 189 received 3 vials, 552 received 4 vials, and 42 received 6–8 vials, 3 patients had dose information missing.

2.3. Data collection

The data were electronically collected by participating hospitals, stored in the registry following standardized protocols and were retrieved for the analysis. Patient age, sex, diagnosis, and comorbidities were extracted from the registry. The results of liver function tests before and after PPC treatment were obtained. The parameters evaluated included serum ALT levels, AST levels, GGT levels, total bilirubin levels, prothrombin activity (PTA) and albumin levels. The PPC doses received were also recorded.

2.4. Statistical analysis

The baseline characteristics of the analysis cohort are presented as the means±standard deviations for continuous variables or as frequencies and percentages for categorical variables. Linear mixed-effects growth curve analysis was used to model the changes in liver function after 2 weeks of PPC treatment[16]. Growth curve modeling is widely applied to analyze individual trajectories. This approach offers greater statistical power and flexibility to accommodate unequally spaced time points and partial missing data[17], features typical of real-world observational datasets. A random intercept is used in this method to account for the within-subject correlations between repeated tests. All available data were included in the analysis. Time, disease and time-by-disease interaction effects were the fixed effects used to examine the heterogeneity of treatment efficacy in different diseases. The model was controlled for age, sex, and hypertension. The impact of treatment dose was analyzed in a similar fashion. Maximum likelihood estimation method was used, which is equal robust to missing data as multiple imputation method[18]. The linearity and normality assumptions were virtually inspected using residual plots. Since this is an exploratory analysis on secondary data, there is no correction for multiple comparisons[19,20]. Two-sided *P* values <0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 1 454 patients were included in the analysis cohort. The average age was (52.1±15.1) years, and the majority of patients were male (63.8%). The patients received a median of 9 (5–13) days of PPC treatment. Patient characteristics and diagnoses are summarized in Table 1. The patients had elevated liver enzyme levels at baseline, with a median ALT level of 78.0 (55.2–154.0) U/L, AST level of 76.0 (54.3–132.5) U/L, and GGT level of 136.0 (89.0–260.0) U/L.

Table 1. Baseline characteristics of analysis cohort.

Characteristics	N=1454
Age, years, mean±SD	52.1±15.1
Sex	
Female	527 (36.2)
Male	927 (63.8)
Treatment duration, days, median (IQR)	9 (5–13)
Hypertension	276 (19.0)
Obesity	3 (0.2)
PPC dosage	
232.5 mg (1 vial)	15 (1.0)
465.0 mg (2 vials)	653 (44.9)
697.5 mg (3 vials)	189 (13.0)
930.0 mg (4 vials)	552 (38.0)
1 395.0–1 860 mg (6–8 vials)	42 (2.9)
HAV or HCV infection	19 (1.2)
Drug-induced liver injury	31 (2.1)
Alcoholic liver disease	52 (3.5)
Autoimmune hepatitis	17 (1.2)
Cirrhosis	117 (8.0)
Nonalcoholic steatohepatitis	64 (4.4)
Hepatocellular carcinoma	211 (14.5)
Non-liver cancers	415 (28.5)

PPC: polyene phosphatidylcholine; HAV: hepatitis A virus; HCV: hepatitis C virus. Data were expressed as n (%), unless otherwise indicated.

3.2. The average hepatoprotective effects of PPC in the cohort

PPC treatment effectively reversed elevated liver enzyme levels (Table 2). The ALT level was reduced by 8.99 U/L per day (95% *CI* -10.20 to -7.77, *P*<0.001), representing a 53.90 U/L reduction in 1 week and a 117.00 U/L reduction in 2 weeks. On average, patients returned to a normal ALT level within 11.2 days. The slope for AST changes was -7.14 U/L per day (-8.24 to -6.03, *P*<0.001), and that for GGT was -6.46 U/L per day (-7.61 to -5.31, *P*<0.001). Total bilirubin levels decreased by 0.91 μmol/L per day (-1.69 to -0.13, *P*<0.05) after PPC treatment. PTA and albumin levels were not impacted by PPC (*P*>0.05).

Table 2. The hepatoprotective effects of polyene phosphatidylcholine on the overall cohort.

Parameters	Baseline	1 week	2 week	Slope	95% LCI	95% UCI	P value
ALT, U/L	141.10	87.20	24.10	-8.99	-10.20	-7.77	<0.001
AST, U/L	114.80	72.00	22.00	-7.14	-8.24	-6.03	<0.001
GGT, U/L	209.90	171.20	125.90	-6.46	-7.61	-5.31	<0.001
Total bilirubin, μ M/L	57.52	52.05	45.72	-0.91	-1.69	-0.13	<0.050
PTA, %	90.05	90.27	90.53	0.04	-0.18	0.25	0.74
Albumin, g/L	35.70	35.60	35.50	-0.01	-0.04	0.03	0.72

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; PTA: prothrombin activity; LCI: lower; UCI: Upper confidence limit.

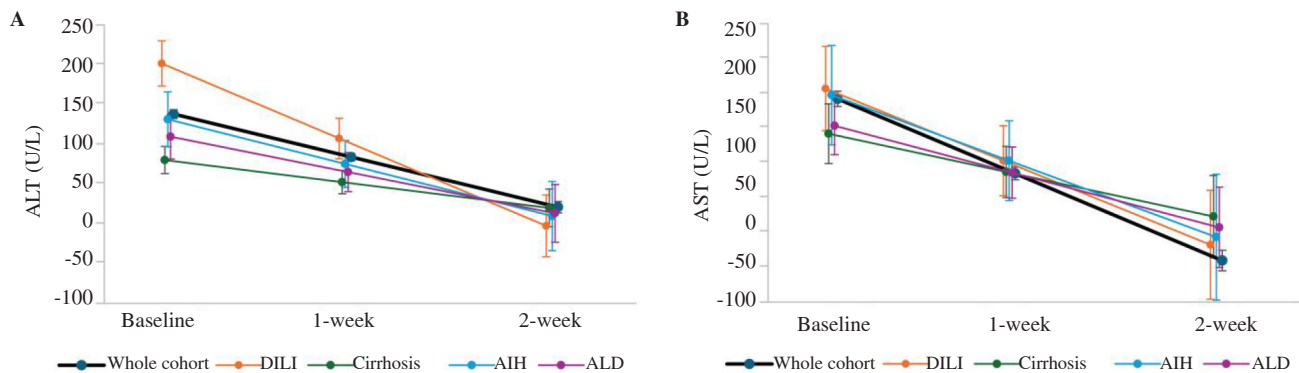


Figure 2. Change of ALT and AST levels in patients with chronic liver diseases. (A) PPC treatment lowered the ALT level in patients with different chronic liver diseases. (B) PPC treatment lowered the AST level in patients with different chronic liver diseases. Least square means at each time point and standard errors from mixed effects growth curve analysis were used for plot. Disease type and sample size included: AIH ($n=17$), ALD ($n=51$), cirrhosis ($n=117$), DILI ($n=31$). PPC: polyene phosphatidylcholine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AIH: autoimmune hepatitis; ALD: alcoholic liver disease; DILI: drug-induced liver injury.

3.3. Heterogeneous effects of PPC treatment

Patients with DILI had significantly higher ALT levels at baseline (204.60 *vs.* 138.40 U/L, $P<0.05$), and their ALT level declined significantly faster than that without DILI (-15.70 U/L *vs.* -8.70 U/L per day, $P<0.05$) during PPC treatment (Figure 2). However, the time to return to normal ALT levels appeared to be similar (10.5 days *vs.* 11.3 days). AST levels decreased by 6.9 U/L per day, and GGT levels decreased by 5.7 U/L per day in patients with DILI, which were not significantly different from those in patients without DILI (Supplementary Table 1).

ALT, AST, and GGT levels were significantly lower in patients with cirrhosis at baseline and decreased more slowly during PPC treatment than in those without cirrhosis (ALT, -4.6 *vs.* -9.4 U/L per day, $P<0.05$; AST, -3.7 *vs.* -7.6 U/L per day, $P<0.05$; GGT, -0.8 *vs.* -7.0 U/L per day, $P<0.01$) (Figure 3 and Supplementary Table 1).

The ALT level decreased by 9.4 U/L per day and the AST level

decreased by 6.3 U/L per day in patients with AIH during PPC treatment, which were not significantly different from those in patients without AIH (Supplementary Table 1). The GGT level in patients with AIH showed almost no decrease during PPC treatment, whereas the decrease was more pronounced in patients without AIH (0.9 *vs.* -6.7 U/L per day, $P<0.05$).

The ALT level decreased by 7.4 U/L per day, and the AST level decreased by 4.5 U/L per day in patients with ALD during PPC treatment, which were not significantly different from that in patients without ALD (Supplementary Table 1). Notably, we observed that ALD patients had a faster decline in GGT levels than other patients did (-16.1 *vs.* -6.1 U/L per day, $P<0.001$).

The ALT level decreased by 6.2 U/L per day, the AST level decreased by 15.5 U/L per day, and the GGT level decreased by 2.0 U/L per day in patients with HAV or HCV infection during PPC treatment; these values were not significantly different from those of other patients (Supplementary Table 1).

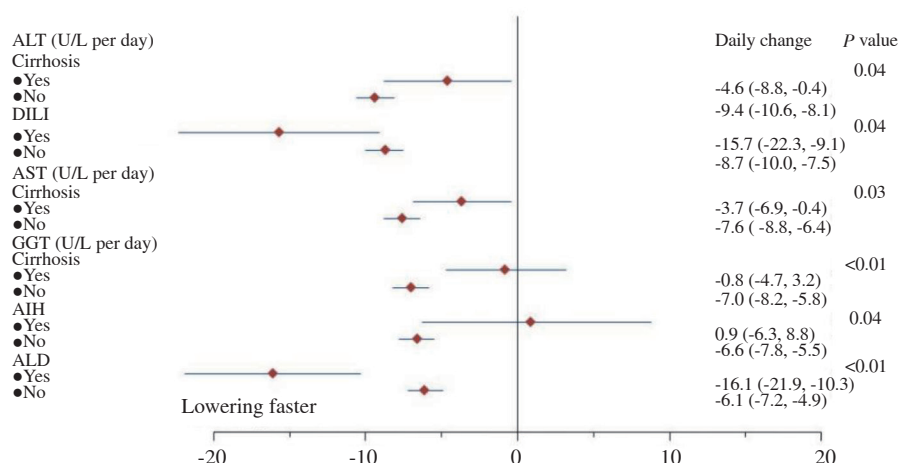


Figure 3. Forest plot illustrates the effect modification on the daily change in liver enzymes (*i.e.* slope) by different chronic liver diseases. Sample sizes of each disease are same as those in Figure 1. The slopes and 95% confidence intervals are estimated using mixed effects growth curve models. *P* values indicate the significant effect modification. ALT: alanine aminotransferase; DILI: drug-induced liver injury; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; AIH: autoimmune hepatitis; ALD: alcohol-related liver disease.

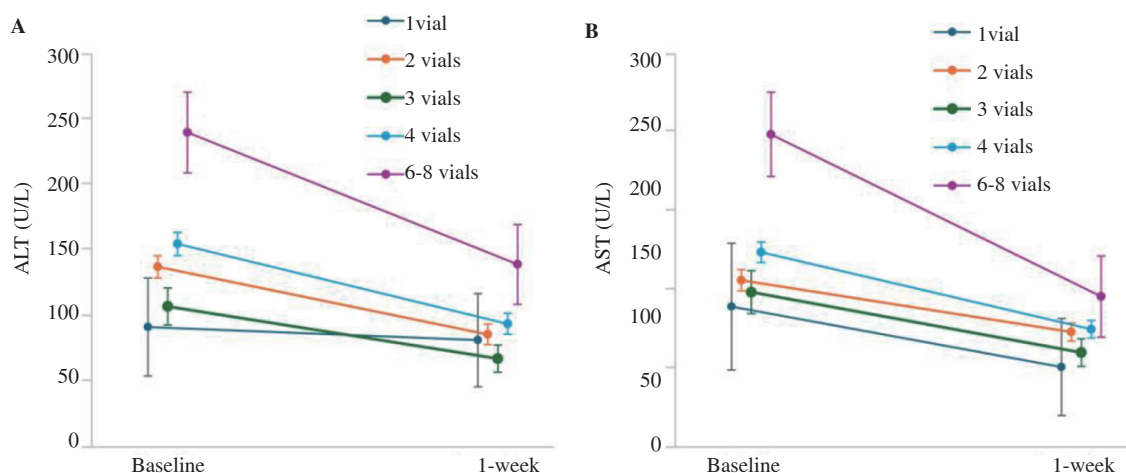


Figure 4. Dose effect on the change of ALT (A) and AST (B) level in patients with PPC regimens. Data points are the least square means and standard errors estimated from mixed effects growth curve model. Each vial contains 232.5 mg PPC. Sample size: 1 vial: $n=15$; 2 vials: $n=653$; 3 vials: $n=189$; 4 vials: $n=552$; 6-8 vials: $n=42$. ALT: alanine aminotransferase; AST: aspartate aminotransferase; PPC: polyene phosphatidylcholine.

The ALT level was reduced by 10.7 U/L per day, whereas the AST level was decreased by 8.1 U/L per day and the GGT level was decreased by 1.24 U/L per day in individuals undergoing PPC therapy for NASH; these differences were not significantly different from the remaining patient cohort (Supplementary Table 1).

The reduction in ALT levels was 6.5 U/L per day, AST levels decreased by 8.5 U/L per day, and GGT levels decreased by 9.1 U/L per day in patients with HCC. These changes did

not significantly differ from those in patients without HCC (Supplementary Table 1).

During cancer treatment, patients with non-liver cancers may experience liver injury. In response to the administration of PPC, the ALT level decreased by 7.9 U/L per day, the AST level decreased by 5.7 U/L per day, and the GGT level decreased by 5.2 U/L per day; these values were not significantly different from those of other patients (Supplementary Table 1).

3.4. Effects of different PPC dose regimens

Patients with higher baseline ALT levels received higher doses of treatment. Single-vial (232.5 mg) treatment was used to treat patients with an average baseline ALT level of 91.5 U/L, whereas 6-8 vials (1 395.0-1 860.0 mg) were used for patients with a baseline ALT level of 239.9 U/L. However, the duration for ALT levels to return to normal was consistent across various dose regimens (11.4, 10.2, 11.3, and 11.9 days for 2, 3, 4, and 6-8 vials, respectively). The only exception was the single-vial treatment, which took patients one month to recover to normal ALT levels (Figure 4A; Supplementary Table 2).

Patients treated with 6-8 vials had the highest baseline AST level (198.7 U/L), compared with 89.3 U/L for patients on a single-vial regimen and 106.0 U/L for patients on a 2-vial regimen. In one week, treatment with 6-8 vials resulted in a 103.1 U/L reduction in AST levels, which was a greater reduction in AST levels than that resulting from treatment with 2 vials (-32.9 U/L) and 4 vials (-48.9 U/L). Patients on a single-vial treatment took 7.7 days to return to normal, and patients treated with 2, 3, 4 and 6-8 vials took 12.0, 9.1, 10.3 and 9.2 days to recover, respectively. Notably, although the baseline AST level among patients treated with 6-8 vials was more than double that of single-vial-treated patients, the time needed to return to normal was similar (Figure 4B, Supplementary Table 2).

4. Discussion

Real-world evidence derived from electronic health records serves as a valuable complement to randomized controlled trial findings[21]. Currently, PPC is extensively used in China to treat patients with liver diseases. We have previously presented real-world evidence on the efficacy of PPC in reducing ALT and AST levels in patients with HBV infection, and the results were similar to those of traditional treatments involving glutathione and magnesium isoglycyrrhizinate. However, in the real-world clinical setting, heterogeneity in treatment efficacy may arise as a result of the diverse mechanisms of liver injury in patients with different liver diseases. This study aimed to further investigate the heterogeneous therapeutic efficiency of PPC in other liver diseases in addition to HBV infection and assess the effects of varying doses. It is important to identify potential effects that warrant more rigorous future investigations[22].

In the entire cohort, PPC treatment significantly lowered ALT (-9.0 U/L per day), AST (-7.0 U/L per day), GGT (-6.0 U/L per day), and total bilirubin levels (-0.9 μ mol/L per day) without

impacting PTA and albumin levels. The results of this analysis are mostly consistent with our previous report[14]. We used data up to two weeks in the analysis rather than 30 days to reduce the potential bias from a few patients who had long-lasting PPC treatment for up to 1 month. This change avoided the drawbacks of uneven time frames in the growth curve analysis[23].

Our study observed that patients with DILI demonstrated an accelerated decrease in ALT levels. There are two possible mechanisms of DILI, either idiosyncratic or intrinsic. The former is caused primarily by reactive metabolites from the causative drug. The resulting oxidative stress damages the membranes of hepatocytes[5]. PPC is an active ingredient of essential phospholipids that is critical for liver cell repair and regeneration as a component of antioxidants[12,24,25]. A study has shown the success of using the combination of PPC, GSH, glycyrrhizin and S-adenosylmethionine to treat children with DILI[11]. A retrospective study in China also provided evidence supporting PPC's efficacy in adults[5]. Our results aligned with these findings and suggest that PPC is effective in lowering elevated ALT levels in DILI patients.

Compared with other patients, patients with cirrhosis presented slower decreases in ALT and AST levels after PPC treatment. Cirrhosis is the progressive consequence of liver fibrosis. Antifibrotic agents or strategies are essential to treat cirrhosis[26]. PPC has antifibrotic effects, as it inhibits the activation of hepatic stellate cells in cell culture and in animal models[27]. This hepatoprotective effect is different from its antioxidant benefit. This may explain the different responses to PPC between patients with DILI and those with cirrhosis. Cirrhosis is an advanced manifestation of long-term liver injury, and the liver may be in an active inflammatory phase or a stable compensated phase. In this study, patients with cirrhosis exhibited milder baseline liver enzyme abnormalities. Although PPC remained effective in this population, its therapeutic effect proceeded more slowly.

PPC did not lower the GGT levels in patients with cirrhosis or AIH. In contrast, patients with ALD presented accelerated normalization of GGT levels. These results suggest that the mechanism through which GGT levels increase among these patients may differ. Similar differences were also observed in COVID-19 associated liver injury[28]. The underlying mechanism is worthy of further investigation. Patients with HAV or HCV infection presented a marked decrease in GGT levels (-15.5 U/L per day). Owing to the limited number of these patients in the analyzed cohort, no significant differences were observed compared with the other patients. Further studies in larger sample cohorts are needed.

In this study, patients with NASH presented decreased levels of ALT (-10.7 U/L per day), AST (-8.1 U/L per day), and GGT

(-1.2 U/L per day) during PPC treatment, which is in line with the results of other studies[7]. This study showed that PPC had significant ameliorative effect on the hepatic malondialdehyde and superoxide dismutase in methionine-choline-deficient diet induced NASH model[29]. Cellular and animal studies have also confirmed that PPC downregulates hepatocyte CYP2E1 expression and associated hepatotoxicity and attenuates oxidative stress, apoptosis, lipoprotein oxidation, and steatosis in nonalcoholic liver injury[27]. Recent studies found the inflammasome played a critical role in NASH pathogenesis[30], and PPC's anti-inflammatory effect may interrupt the disease progression. In addition, PPC reduces liver enzyme levels in patients with HCC. Studies have shown that PPC can increase the sensitivity of cancer cells to radiotherapy/chemotherapy, improve therapeutic efficacy, and inhibit experimental hepatocarcinogenesis[27].

Non-liver cancer patients often experience liver injury due to various factors, such as chemotherapy-related toxicities, radiation, and the physiological strain of surgical interventions[31,32]. The study cohort of non-liver cancer patients included individuals who had been diagnosed with gastric cancer, lung cancer, or colorectal cancer. The results showed that PPC effectively lowered the levels of liver enzymes in non-liver cancer patients with liver injury, especially in gastric cancer patients with reduced ALT levels.

Dose analysis suggested that clinicians were likely to determine the doses of prescribed medication on the basis of serum ALT and AST levels at diagnosis. The efficacy of PPC in treating liver injury was dose-dependent in terms of the slope of the reduction. However, this needs to be interpreted with caution because the effect was confounded by baseline enzyme levels. Patients with higher baseline ALT levels received higher doses of treatment; however, the duration for ALT levels to return to normal was consistent across various dose regimens. This means that patients with severe liver injury who receive high doses of PPC benefit from shorter hospital stays and savings in health care costs.

This study is strengthened by its utilization of real-world data and sophisticated statistical analysis methods. There are also several limitations. The first blood test for liver function was not performed daily for every patient, resulting in unequally-spaced time points of data. However, this limitation can be overcome by using growth curve analysis methods. Second, some groups had a small sample size. A lack of power to examine heterogeneity for some diseases, such as HAV/HCV, was possible. Third, since these are registry-derived data, the purpose of the registry might not perfectly fit the needs of the analysis. The purpose of the registry might not perfectly fit the needs of the analysis. Therefore, some important information is not available, such as the cause of DILI, the stage of

NASH and previous treatments received. Another limitation is the absence of treatment control groups, which could make our findings about PPC more robust, although we have reported the comparison of PPC with GSH and magnesium isoglycyrrhizinate in a previous publication. However, as an exploratory observational study, these results warrant further confirmation in future studies.

After undergoing PPC treatment, the serum levels of ALT and AST in patients with liver injury decreased to differing extents, demonstrating different trajectories through the course of treatment for different liver diseases.

Conflict of interest statement

Authors declare no conflict of interest for this article.

Ethics approval and consent to participate

The research was approved by the Ethics Committee at Peking University First Hospital (No. 2021-434; approval date: November 8, 2021) and conducted according to the principles expressed in the Declaration of Helsinki. The requirement for informed consent for this study was waived, and approval was granted by the Ethical Committee at Peking University First Hospital.

Data availability

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

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Authors' contributions

YFH, NL, YYY and YXX contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

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