

Original Article

Ademetionine 1,4-butanedisulfonate plus dexamethasone for cholestatic hepatitis: therapeutic efficacy and risk factors

Qiong Mo*, Dena Kong*, Le Song, Lijun He, Yanqiong Zhang, Xiaowen Guo, Bo Zhang

Department of Infectious Diseases, General Hospital of Central Theater Command, Wuhan 430070, Hubei, China.

*Equal contributors and co-first authors.

Received May 18, 2026; Accepted August 14, 2026; Epub September 15, 2026; Published September 30, 2026

Abstract: This retrospective study analyzes how patients with cholestatic hepatitis (CH) have responded to the dual-drug therapy consisting of Ademetionine 1,4-Butanedisulfonate (SAmE-BD) and Dexamethasone (DEX) and discusses the associated risk factors. First, we enrolled 128 CH patients admitted to our hospital (July 2022-July 2025), with 60 patients in the control group receiving SAmE-BD, and the remaining 68 cases in the research group receiving SAmE-BD+DEX. We then conducted comparative assessments of the following outcome measures: therapeutic efficacy, safety (nausea, diarrhea, insomnia, myalgia), symptom relief (fatigue, itching), liver function (total bilirubin [TBIL], alanine transaminase [ALT], alkaline phosphatase [ALP], γ -glutamyltransferase [GGT]), inflammation (interleukin [IL]-6, tumor necrosis factor [TNF- α]), fibrosis markers (type III procollagen peptide [PCIII], hyaluronic acid [HA], laminin [LN]), and serum lipid profiles (total cholesterol [TC], triglyceride [TG], low-density lipoprotein cholesterol [LDL-C]). Significant clinical correlates of therapeutic efficacy were analyzed using univariate and multivariate approaches. In the research group, markedly greater overall efficacy was observed compared to controls, alongside an equivalent incidence of total adverse reactions, significantly better symptom relief, and notably lower post-treatment levels of indices associated with liver function, inflammation, fibrosis, and blood lipids. Through further analysis, diabetes comorbidity, ALP, and therapeutic method were identified as independent determinants of therapeutic efficacy in CH patients. These findings support the role of SAmE-BD+DEX in significantly enhancing therapeutic effectiveness in CH patients. Also, the risk of treatment ineffectiveness is heightened in patients presenting with diabetes or high pre-treatment ALP, as well as in those using SAmE-BD alone.

Keywords: Ademetionine 1,4-butanedisulfonate, dexamethasone, cholestatic hepatitis, therapeutic efficacy, risk factor

Introduction

Cholestatic liver disease, mainly presenting as cholestasis, can progress to hepatitis with cholestasis, liver fibrosis, cirrhosis, and even liver failure [1]. Hepatitis with cholestasis, or cholestatic hepatitis (CH), is essentially a disorder of bile secretion at the level of bile canaliculi or hepatocytes, which can be clinically manifested as fatigue, itchy skin, gray stool, yellow urine, and hepatomegaly [2, 3]. The disease is multifarious in pathogenesis, with viral infection (especially hepatitis B and E viruses) being the primary inducement [4]. Acute viral hepatitis-associated CH can further exacerbate patients' clinical symptoms; however, debate persists

regarding the optimal treatment strategy [5]. The current mainstay therapies, represented by antiviral agents, immunosuppressants, and/or medications for symptom management, all carry adverse events like increased infection risk, metabolism abnormalities, and even the development of antiviral resistance, making it pressing to explore well-tolerated and effective treatment schemes to manage CH [6].

As a natural compound, Ademetionine 1,4-Butanedisulfonate (SAmE-BD) can be applied to hepatopathy treatment, helping alleviate liver dysfunction and hepatitis and is associated with a low incidence of adverse events [7]. Despite its certain clinical safety, SAmE-BD

may cause gastrointestinal discomfort (e.g., diarrhea, abdominal pain, nausea), though these are generally mild in severity [8]. As pointed out by Qiao et al. [9], SAMe-BD for viral hepatitis patients accelerates their recovery from the disease, inhibits serum inflammation, and reduces liver function impairment. Dexamethasone (DEX), an extensively used glucocorticoid, is mainly metabolized by CYP3A4 in the liver. Its application to hepatopathy patients is associated with a lowered metabolic clearance rate and an extended plasma half-life [10]. In a basic study, low-dose DEX pretreatment of mesenchymal stem cells can enhance its paracrine therapeutic effects on liver diseases, including the inhibition of hepatocellular carcinoma cell proliferation and amelioration of acute liver failure, suggesting that DEX may have extensive clinical application value in liver disease treatment [11]. Its efficacy on CH has been verified in rat experiments, where it acts as a positive control drug to significantly improve liver function indices and alleviate pathologic manifestations of liver tissue in model rats [12].

Given the paucity of existing investigations into the therapeutic role of SAMe-BD+DEX in CH treatment, as well as the limited understanding of the risk determinants, this study attempted to carry out relevant research to fill the relevant clinical gaps and provide a new optimization scheme for the treatment of such patients.

Materials and methods

General information

In this retrospective analysis, the study cohort was composed of 128 CH patients seeking medical services at our center from July 2022 to July 2025. Sixty of them receiving SAMe-BD formed the control group; the remaining sixty-eight cases constituted the research group managed with SAMe-BD+DEX. The study was conducted after securing approval from the General Hospital of Central Theater Command Ethics Committee. Clinical comparability of the study cohorts was confirmed by their balanced distributions in baseline data ($P>0.05$).

Patient enrollment criteria

The inclusion criteria were as follows: diagnosis of cholestatic viral hepatitis [13]; adults (age

range: 18-80); receiving treatment for the first time; non-pregnant or lactating women; having normal communication and cognitive abilities; and possessing intact clinical data.

Study exclusion was indicated if any of the following were met: drug-induced, alcohol-associated, autoimmune, genetic, or pregnancy-induced cholestatic hepatitis; Child-Pugh grade C of liver function; extrahepatic bile duct stones/obstruction; serious diseases of the heart, brain, or kidneys; malignant tumors; portal hypertension, ascites, and other decompensated manifestations of cirrhosis; contraindications to the studied drugs; infections or coagulation disorders; serious diseases of the endocrine, respiratory, nervous, or circulatory system; mental illness.

Treatment methods

All patients received routine basic treatments after admission, including bed rest, a low-fat diet, liver protection and enzyme reduction, symptomatic support, electrolyte disorder correction, and antiviral therapy.

Control group: SAMe-BD for injection was administered by dissolving 1.0 g of the drug in 250 mL of 5% glucose solution for intravenous infusion, once daily. The treatment was continued for 2 to 4 weeks.

Research group: DEX Sodium Injection was supplemented in addition to the above treatment. 5-10 mg of DEX was infused into 100 mL of normal saline for intravenous infusion, once daily. The dosage was gradually reduced following 3-5 days of continuous treatment, depending on the patient's liver function and symptoms, with the total course of hormone treatment not exceeding 2 weeks. The treatment course was identical across the groups. Liver function-associated indices were reexamined upon treatment completion to evaluate therapeutic efficacy.

Outcome measures

Therapeutic efficacy. Efficacy was evaluated as markedly effective (complete resolution of symptoms after treatment, like fatigue and itching, with normalized liver function indices), effective (symptom alleviation and significant improvements in liver function indices), or inef-

Table 1. Baseline patient data

Category	Control group (n=60)	Research group (n=68)	t/ χ^2	P
Sex			0.078	0.780
Male	35 (58.33)	38 (55.88)		
Female	25 (41.67)	30 (44.12)		
Age (years)	52.08±6.39	53.97±6.68	1.630	0.106
Disease duration (months)	11.98±2.37	11.26±2.96	1.506	0.135
Comorbid hypertension	17 (28.33)	20 (29.41)	0.018	0.893
Comorbid diabetes	10 (16.67)	12 (17.65)	0.022	0.883
Comorbid chronic obstructive pulmonary disease	8 (13.33)	13 (19.12)	0.778	0.378
Disease type			0.857	0.836
Cholestatic hepatitis C	5 (8.33)	6 (8.82)		
Cholestatic hepatitis B	36 (60.00)	39 (57.35)		
Hepatitis B complicated by hepatitis E-induced cholestasis	5 (8.33)	9 (13.24)		
Cholestatic hepatitis E	14 (23.33)	14 (20.59)		

fective (non-significant changes in symptoms and liver function indexes from baseline following treatment completion). Total effective rate = (markedly effective cases + effective cases)/total cases.

Safety. It was assessed by recording the occurrences of adverse drug reactions (ADRs), including nausea, diarrhea, insomnia, and myalgia, across the groups and computing the incidence.

Symptom relief. It was assessed by observing and recording the relief of fatigue and itching after treatment.

Liver function. Before and after the intervention, both patient groups received a venipuncture for venous blood collection (4 mL) during morning hours on an empty stomach. Following centrifugation-based serum isolation, total bilirubin (TBIL), alanine transaminase (ALT), and γ -glutamyltransferase (GGT) were detected by the kinetic method, and alkaline phosphatase (ALP) was measured using the disodium phenyl phosphate colorimetric method.

Inflammatory cytokines (ICKs). We performed enzyme-linked immunosorbent assays (ELISAs) to quantify pre- and post-interventional interleukin (IL)-6 and tumor necrosis factor (TNF)- α levels in patients' serum samples.

Fibrosis markers. ELISAs were carried out for serum type III procollagen peptide (PCIII), hyal-

uronic acid (HA), and laminin (LN) measurements before and after intervention.

Serum lipids. Using an automatic biochemical analyzer, we determined the levels of total cholesterol (TC), triacylglycerol (TG), and low-density lipoprotein cholesterol (LDL-C) in patients' serum specimens collected prior to and following the intervention.

Statistical analysis

Continuous variables, namely indices associated with liver function, inflammation, liver fibrosis, and lipids, were expressed by the mean $\pm$ SD, with between-group and within-group differences examined using independent samples t-tests and paired t-tests, respectively. Gender, comorbidities (hypertension/diabetes), and other counted data were shown as n (%) and comparatively assessed by the χ^2 test. Through univariate and multivariate analyses, efficacy determinants were explored. In this study, all statistical analyses were executed in SPSS 22.0, employing a $P < 0.05$ significance threshold.

Results

Patient baseline information

The patient cohorts were well balanced in terms of sex, age, disease course, hypertension, diabetes, chronic obstructive pulmonary disease, and disease type ($P > 0.05$), supporting their comparability and feasibility for subsequent research (**Table 1**).

Table 2. Curative effect comparison

Category	Control group (n=60)	Research group (n=68)	χ^2	P
Markedly effective	16 (26.67)	22 (32.35)	7.529	0.006
Effective	29 (48.33)	41 (60.29)		
Ineffective	15 (25.00)	5 (7.35)		
Overall efficacy	45 (75.00)	63 (92.65)		

Table 3. Safety in the two groups

Category	Control group (n=60)	Research group (n=68)	χ^2	P
Nausea	1 (1.67)	1 (1.47)	0.411	0.521
Diarrhea	1 (1.67)	3 (4.41)		
Insomnia	2 (3.33)	2 (2.94)		
Myalgia	1 (1.67)	2 (2.94)		
Total	5 (8.33)	8 (11.76)		

Table 4. Symptom relief of the two groups

Category	Control group (n=60)	Research group (n=68)	χ^2	P
Fatigue				
Pre-treatment	41 (68.33)	48 (70.59)	0.077	0.782
Post-treatment	27 (45.00)	18 (26.47)	4.801	0.028
Itching				
Pre-treatment	32 (53.33)	39 (57.35)	0.208	0.648
Post-treatment	25 (41.67)	16 (23.53)	4.816	0.028

Therapeutic efficacy comparison

Regarding efficacy, 16, 29, and 15 control patients fell into the “markedly effective”, “effective”, and “ineffective” categories, respectively, corresponding to 22, 41, and 5 cases in the research group. The research group had superior overall efficacy to the controls (92.65% vs. 75.00%, $P=0.006$ (**Table 2**).

Safety profile analysis

Nausea, diarrhea, insomnia, and myalgia developed in both patient cohorts, with the corresponding number of cases being 1, 3, 2, and 2 in the research group, and 1, 1, 2, and 1 case in the control group, demonstrating no marked inter-group differences in the incidence of total adverse reactions ($P>0.05$; **Table 3**).

Comparative symptom relief assessment

The study groups were similar in the number of fatigue and itching cases before treatment

($P>0.05$); both cohorts showed a reduction in fatigue and itching cases post-treatment, with a more pronounced decrease in the research group ($P<0.05$; **Table 4**).

Liver function analysis

The pre-treatment TBIL, ALT, ALP, and GGT were equivalent across the cohorts ($P>0.05$). The corresponding intervention led to a decreasing trend in all indices in both patient groups, particularly the research group that used the combination therapy ($P<0.05$; **Table 5**).

Comparative evaluation of ICKs

Similar IL-6 and TNF- α were identified in the two groups prior to the intervention ($P>0.05$). Both ICKs exhibited a decline in their levels post-treatment, with even lower expression found in the research group when compared to controls ($P<0.001$; **Table 6**).

Fibrosis marker analysis

PCIII, HA, and LN, indices associated with hepatic fibrosis, were comparable across the cohorts before treatment ($P>0.05$); all the indexes were significantly decreased post-treatment ($P<0.01$), particularly in the research group ($P<0.01$; **Figure 1**).

Serum lipid indices

The groups showed comparability in pre-treatment TC, TG, and LDL-C ($P>0.05$); a treatment-induced reduction in these indexes was noted for both cohorts post-treatment ($P<0.01$), with lower levels observed in the research group compared to the control group ($P<0.01$; **Figure 2**).

Analysis of factors influencing therapeutic efficacy

In the inter-group comparison (effective versus ineffective groups), no significant differences were identified in sex, age, disease course, comorbid hypertension/chronic obstructive pulmonary disease, TBIL, ALT, GGT, IL-6, PCIII, HA, LN, TC, TG, or LDL-C ($P>0.05$), while statisti-

Table 5. Hepatic function assessment

Category	Control group (n=60)	Research group (n=68)	t	P
Category				
TBIL (μmol/L)				
Pre-treatment	95.88±29.19	100.07±39.44	0.676	0.501
Post-treatment	57.67±17.37	49.40±15.41	2.854	0.005
ALT (U/L)				
Pre-treatment	75.45±25.29	76.53±25.01	0.243	0.809
Post-treatment	51.08±14.57	41.79±12.63	3.864	<0.001
ALP (U/L)				
Pre-treatment	393.30±137.44	408.54±156.32	0.582	0.562
Post-treatment	216.55±65.20	179.90±49.11	3.617	<0.001
GGT (U/L)				
Pre-treatment	137.32±57.60	147.82±39.29	1.217	0.226
Post-treatment	115.22±36.39	100.56±35.95	2.289	0.024

Note: TBIL, total bilirubin; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase.

Table 6. Hepatic function assessment

Category	Control group (n=60)	Research group (n=68)	t	P
Category				
IL-6 (pg/mL)				
Pre-treatment	9.95±3.52	10.88±5.22	1.166	0.246
Post-treatment	8.50±2.36	6.37±2.27	5.200	<0.001
TNF-α (pg/mL)				
Pre-treatment	10.82±4.33	11.98±3.70	1.634	0.105
Post-treatment	7.97±2.58	5.61±1.33	6.615	<0.001

Note: IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

cal significance was present regarding comorbid diabetes, disease type, ALP, TNF-α, and therapeutic method ($P<0.05$). In the subsequent multivariate analysis, where all the aforementioned significant factors were incorporated, diabetes comorbidity (OR=4.894, 95% CI: 1.308-18.314, $P=0.018$), ALP (OR=3.706, 95% CI: 1.074-12.784, $P=0.038$), and therapeutic method (OR=0.240, 95% CI: 0.066-0.875, $P=0.031$) were confirmed as independent determinants of therapeutic efficacy. It should be added that the disease type was not an independent influencing factor ($P=0.066$). Although cholestatic hepatitis E showed a trend of poor therapeutic efficacy, the difference was not adjusted for multiple comparisons and was thus not considered an independent risk factor. See **Tables 7, 8**.

Discussion

This study first determined the superiority of the SAMe-BD+DEX combination over SAMe-BD in terms of overall effectiveness in CH manage-

ment (92.65% vs. 75.00%). Similar to our findings, a systematic review pointed out that short-term corticosteroid therapy (prednisolone at 30-60 mg/d) could provide clinical benefits for patients with viral hepatitis-related cholestasis who are refractory to standard treatment [5]. In another case study, oral steroids showed certain clinical effectiveness in treating long-term cholestasis jaundice after hepatitis A

infection, suggesting a potential alternative when other treatments fail to relieve symptoms [14]. The therapeutic mechanism of SAMe-BD in CH may be related to its methylation of phospholipids, which may exert therapeutic effects by normalizing hepatic transmethylation and transsulfuration activities [15]. DEX, by resisting hepatitis and oxidative stress by androgen receptor activation, effectively attenuates cholestasis-related inflammation and oxidative stress [16]. The two, when combined to treat CH patients, can enhance therapeutic effects by mediating distinct pathways, thus boasting a curative effect significantly outperforming SAMe-BD monotherapy. Besides, although DEX was added in the combined regimen discussed herein, the total risk of adverse reactions was not significantly elevated, suggesting that the combined regimen was generally well tolerated. This may be related to DEX's induction of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), which may theoretically accelerate the metabolic clearance of co-administered drugs and reduce their accumula-

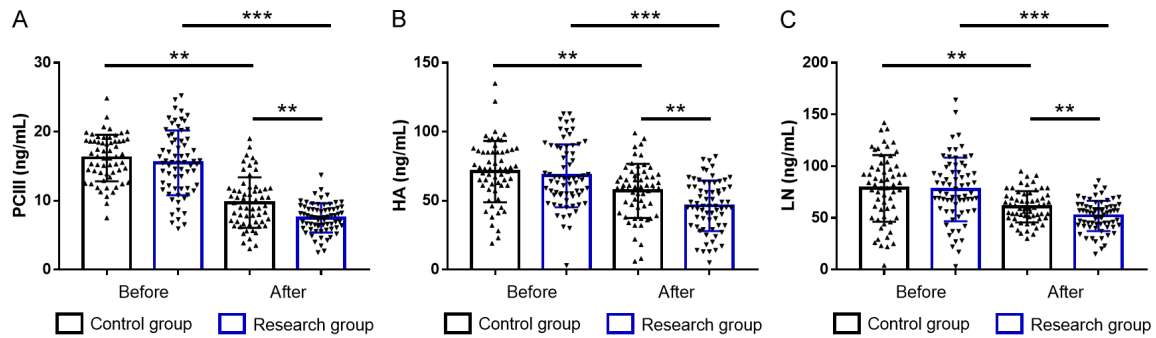


Figure 1. Comparative analysis of fibrosis indices. A. Type III procollagen peptide (PCIII) changes pre- and post-treatment. B. Hyaluronic acid (HA) changes pre- and post-treatment. C. Pre- and post-treatment laminin (LN) across groups. Note: ** $P < 0.01$; *** $P < 0.001$.

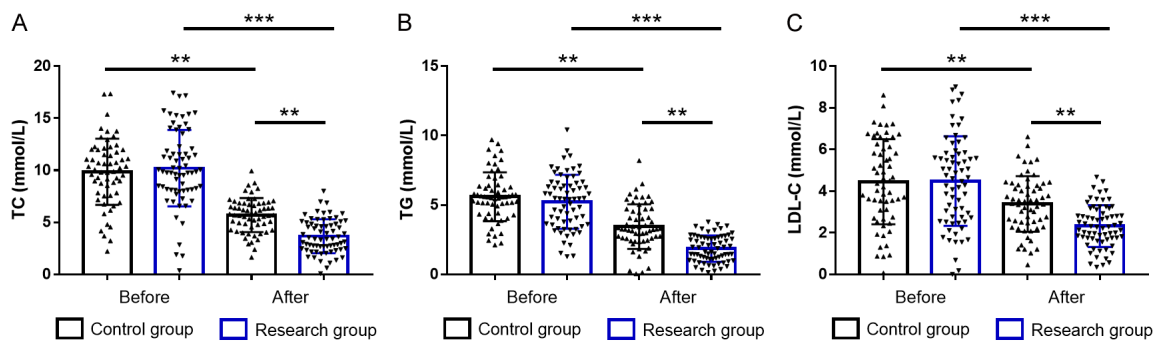


Figure 2. Serum lipid indices across groups. A. Total cholesterol (TC) changes pre- and post-treatment. B. Pre- and post-treatment alterations in triglyceride (TG). C. Low-density lipoprotein cholesterol (LDL-C) changes pre- and post-treatment. Note: ** $P < 0.01$; *** $P < 0.001$.

tion, possibly contributing to the acceptable tolerability of the combination. Alternatively, the short treatment course and moderate corticosteroid dose may be the primary factors [17]. Masrou et al. [18] reported that DEX, when applied to liver cirrhosis patients undergoing transcatheter arterial chemoembolization, can effectively reduce the incidence of fever and encephalopathy on the second day following the operation, supporting DEX's certain clinical safety and thus lending support to our results. According to the American Gastroenterological Association (AGA) guidelines on HBV reactivation, the risk associated with corticosteroid use is determined primarily by the dose, duration of treatment, and the patient's HBV serological status (HBsAg and anti-HBc). For HBsAg-positive patients, a prednisone-equivalent dose of ≥ 20 mg/day for ≥ 4 weeks is considered high risk, while a dose of 10-20 mg/day for ≥ 4 weeks is considered moderate risk. In contrast, short-term use (≤ 1 week) at any dose is associated with a very low risk. The regimen

used in this study (prednisone-equivalent dose: 33-67 mg/day; total duration: < 2 weeks) falls between the ≤ 1 -week very-low-risk category and the ≥ 4 -week moderate/high-risk categories. Therefore, our regimen should be interpreted as low-to-moderate risk, rather than simply "very low risk" [19].

Statistics on clinical symptoms indicated that adding DEX on the basis of SAMe-BD helped relieve fatigue and itching symptoms more significantly. DEX has been shown to be effective in reducing nitric oxide production and down-regulating inducible nitric oxide synthase (iNOS) expression by inhibiting nuclear factor κB (NF- κB) and Toll-like receptor 4 (TLR4) signaling, while also modulating the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, thereby reducing inflammatory responses and effectively alleviating clinical symptoms such as fatigue and itching [20]. The addition of DEX also reduced liver function damage by more pronouncedly

Table 7. Efficacy determinants (univariate analysis)

Category	Ineffective group (n=20)	Effective group (n=108)	χ^2	P
Sex			0.040	0.842
Male (n=73)	11 (55.00)	62 (57.41)		
Female (n=55)	9 (45.00)	46 (42.59)		
Age (years)			0.557	0.456
<53 (n=61)	8 (40.00)	53 (49.07)		
≥53 (n=67)	12 (60.00)	55 (50.93)		
Disease duration (months)			0.093	0.761
<12 (n=60)	10 (50.00)	50 (46.30)		
≥12 (n=68)	10 (50.00)	58 (53.70)		
Comorbid hypertension (n=37)	7 (35.00)	30 (27.78)	0.428	0.513
Comorbid diabetes (n=22)	8 (40.00)	14 (12.96)	8.667	0.003
Comorbid chronic obstructive pulmonary disease (n=21)	5 (25.00)	16 (14.81)	1.276	0.259
Disease type			Fisher's exact test	0.005
Cholestatic hepatitis C (n=11)	3 (15.00)	8 (7.41)		
Cholestatic hepatitis B (n=75)	5 (25.00)	70 (64.81)		
Hepatitis B complicated by hepatitis E-induced cholestasis (n=14)	4 (20.00)	10 (9.26)		
Cholestatic hepatitis E (n=28)	8 (40.00)	20 (18.52)		
TBIL (μmol/L)			2.133	0.144
<100.50 (n=64)	7 (35.00)	57 (52.78)		
≥100.50 (n=64)	13 (65.00)	51 (47.22)		
ALT (U/L)			0.033	0.855
<74.00 (n=60)	9 (45.00)	51 (47.22)		
≥74.00 (n=68)	11 (55.00)	57 (52.78)		
ALP (U/L)			5.926	0.015
<393.50 (n=64)	5 (25.00)	59 (54.63)		
≥393.50 (n=64)	15 (75.00)	49 (45.37)		
GGT (U/L)			0.169	0.681
<149.00 (n=63)	9 (45.00)	54 (50.00)		
≥149.00 (n=65)	11 (55.00)	54 (50.00)		
IL-6 (pg/mL)			1.444	0.230
<10.00 (n=54)	6 (30.00)	48 (44.44)		
≥10.00 (n=74)	14 (70.00)	60 (55.56)		
TNF-α (pg/mL)			5.926	0.015
<11.97 (n=64)	5 (25.00)	59 (54.63)		
≥11.97 (n=64)	15 (75.00)	49 (45.37)		
PCIII (ng/mL)			0.237	0.626
<15.76 (n=64)	9 (45.00)	55 (50.93)		
≥15.76 (n=64)	11 (55.00)	53 (49.07)		
HA (ng/mL)			0.948	0.330
<67.50 (n=64)	8 (40.00)	56 (51.85)		
≥67.50 (n=64)	12 (60.00)	52 (48.15)		
LN (ng/mL)			0.169	0.681
<79.00 (n=63)	9 (45.00)	54 (50.00)		
≥79.00 (n=65)	11 (55.00)	54 (50.00)		
TC (mmol/L)			0.237	0.626
<9.97 (n=64)	11 (55.00)	53 (49.07)		
≥9.97 (n=64)	9 (45.00)	55 (50.93)		
TG (mmol/L)			0.806	0.369
<5.49 (n=63)	8 (40.00)	55 (50.93)		
≥5.49 (n=65)	12 (60.00)	53 (49.07)		

SAMe-BD and dexamethasone for cholestatic hepatitis

LDL-C (mmol/L)			0.237	0.626
<4.55 (n=64)	9 (45.00)	55 (50.93)		
≥4.55 (n=64)	11 (55.00)	53 (49.07)		
Therapeutic method			7.529	0.006
Ademetionine 1,4-butanedisulfonate (n=60)	15 (75.00)	45 (41.67)		
Ademetionine 1,4-butanedisulfonate plus dexamethasone (n=68)	5 (25.00)	63 (58.33)		

Note: TBIL, total bilirubin; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, γ -glutamyltransferase; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α ; HA, hyaluronic acid; LN, laminin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol.

Table 8. Determinants of curative effects (multivariate analysis)

Category	B	SE	WALD	P	OR	95% CI
Comorbid diabetes	1.588	0.673	5.562	0.018	4.894	1.308-18.314
Disease type			7.184	0.066		
Hepatitis C vs. hepatitis B	1.954	1.001	3.810	0.051	7.058	0.992-50.224
Superimposed vs. hepatitis B	1.298	0.875	2.203	0.138	3.663	0.660-20.343
Hepatitis E vs. hepatitis B	1.645	0.704	5.460	0.019	5.184	1.304-20.610
ALP (U/L)	1.310	0.632	4.300	0.038	3.706	1.074-12.784
TNF- α (pg/mL)	1.283	0.658	3.807	0.051	3.609	0.994-13.099
Medication regimen	-1.429	0.661	4.672	0.031	0.240	0.066-0.875

Note: Hepatitis B serves as a reference when comparing different disease types. ALP, alkaline phosphatase; TNF- α , tumor necrosis factor- α .

suppressing TBIL, ALT, ALP, and GGT levels. In a rat cholestasis model study, DEX demonstrated efficacy in mitigating cholestatic liver injury and improving liver function by inhibiting intrinsic pathways and enhancing mitochondrial biogenesis, which is consistent with our observations and provides a mechanistic explanation [21]. From the inflammation perspective, DEX supplementation effectively reduced IL-6 and TNF- α expression in patients' serum, and thus significantly inhibited serum inflammation. The anti-inflammatory action of DEX may be attributed to its inhibition of NOD-like receptor pyrin domain-containing protein 3 (NLRP3)/IL-1 β pathway, which results in a significant reduction in the release of IL-6, TNF- α , and other inflammatory mediators [22]. CH patients treated with SAMe-BD+DEX also displayed effective fibrosis reduction, manifested by significantly reduced PCIII, HA, and LN levels post-treatment. In the report of Xu et al. [23], esterase-responsive carbon quantum dot-DEX demonstrated feasibility in anti-hepatic fibrosis treatment by preventing hepatic fibrosis progression through liver injury alleviation and collagen deposition reduction. This partially explains the results of this study while shedding lights on the clinical application of DEX (that is, multiplexing nano-drug targeted thera-

py). Furthermore, SAMe-BD+DEX for CH more effectively improved blood lipid metabolism by reducing TC, TG, and LDL-C, all lipid indices. It is known that SAMe-BD may inhibit fatty acid uptake by regulating the methionine adenosine transferase 2A (MAT2A)-acyl-CoA synthetase long chain family member 4 (ACSL4) metabolic axis. DEX, on the other hand, down-regulates the expression of key genes for cholesterol synthesis, possibly by inhibiting the over-activation of the TNF- α /NF- κ B/sterol regulatory element-binding protein-2 (SREBP2) axis in a cholestatic state. The two agents may act synergistically to ameliorate cholestasis-induced lipid metabolism disorders [24, 25]. In the further analysis of efficacy-associated determinants, diabetes, ALP, and therapeutic method were found to independently influence therapeutic efficacy. This is because diabetes can induce oxidative stress and inflammatory reaction through hyperglycemia, thus aggravating liver damage and affecting the maximum effect of patients [26]. High ALP can reflect the destruction of the bile duct epithelial barrier and the disorder of the inflammatory microenvironment, which is not conducive to the smooth recovery of patients [27]. The addition of DEX to SAMe-BD therapy can synergistically enhance the therapeutic effect to achieve effi-

cacy maximization. Multivariate analysis in this study showed that TNF- α was a borderline significant indicator for efficacy ($P=0.051$), which is inconsistent with the finding by Luan et al., who confirmed that TNF- α was closely related to liver injury and fibrosis in cholestatic liver injury [28]. This suggests that the value of TNF- α as a predictor of therapeutic efficacy needs further verification.

This study had the following limitations that need to be addressed: First, given the absence of virological data, relevant information should be prospectively collected in future studies to further verify the potential clinical impact of the combination drug therapy. The second deficiency was the lack of prognostic evaluation, warranting the supplementation of five-year follow-up analysis to further clarify the effect of the two treatment schemes on patient long-term prognosis. Finally, there was no health economics analysis. Subsequent relevant analyses may contribute to the vigorous promotion of the combined regimen.

In conclusion, SAMe-BD plus DEX demonstrated significant therapeutic efficacy in the treatment of CH without significantly increasing total adverse reactions. This scheme can effectively alleviate fatigue/itching symptoms and liver function damage, effectively inhibit serum inflammation and fibrosis, and improved serum lipid profiles. Additionally, a heightened risk of ineffective treatment was associated with diabetes comorbidity, high baseline ALP, and single use of SAMe-BD.

Disclosure of conflict of interest

None.

Address correspondence to: Bo Zhang, Department of Infectious Diseases, General Hospital of Central Theater Command, Wuhan 430070, Hubei, China. Tel: +86-13871531199; E-mail: Xiabobo@sohu.com

References

[1] Wei C, Qiu J, Wu Y, Chen Z, Yu Z, Huang Z, Yang K, Hu H and Liu F. Promising traditional Chinese medicine for the treatment of cholestatic liver disease process (cholestasis, hepatitis, liver fibrosis, liver cirrhosis). *J Ethnopharmacol* 2022; 297: 115550.

[2] Luo X and Lu LG. Progress in the management of patients with cholestatic liver disease: where are we and where are we going? *J Clin Transl Hepatol* 2024; 12: 581-588.

[3] Grant LM and John S. Cholestatic Jaundice. In: editors. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Savio John declares no relevant financial relationships with ineligible companies.: 2026. pp.

[4] de Moraes ACP, Gouvea MG, Ferreira AC, Pinho JRR, de Mello ES, D'Albuquerque LAC, Terra-buio D, Abdala E, Carrilho FJ and Pessoa MG. The impact of hepatitis E infection on hepatic fibrosis in liver transplanted patients for hepatitis C infection. *Braz J Infect Dis* 2021; 25: 101587.

[5] Giri S, Khatana G, Gore P, Praharaj DL, Kulkarni AV and Anand AC. Therapeutic options for the management of the cholestatic phase of viral hepatitis A and E-A systematic review. *J Clin Exp Hepatol* 2025; 15: 102557.

[6] Wazir H, Abid M, Essani B, Saeed H, Ahmad Khan M, Nasrullah F, Qadeer U, Khalid A, Varrassi G, Muzammil MA, Maryam A, Syed ARS, Shah AA, Kinger S and Ullah F. Diagnosis and treatment of liver disease: current trends and future directions. *Cureus* 2023; 15: e49920.

[7] Baden KER, McClain H, Craig E, Gibson N, Draime JA and Chen AMH. S-Adenosylmethionine (SAMe) for liver health: a systematic review. *Nutrients* 2024; 16: 3668.

[8] Morgan TR, Osann K, Bottiglieri T, Pimstone N, Hoefs JC, Hu KQ, Hassanein T, Boyer TD, Kong L, Chen WP, Richmond E, Gonzalez R, Rodriguez LM and Meyskens FL. A phase II randomized, controlled trial of S-adenosylmethionine in reducing serum alpha-fetoprotein in patients with hepatitis c cirrhosis and elevated AFP. *Cancer Prev Res (Phila)* 2015; 8: 864-872.

[9] Qiao J and Zhao C. Therapeutic effect of adenosylmethionine on viral hepatitis and related factors inducing diseases. *Am J Transl Res* 2021; 13: 9485-9494.

[10] Bourdin V, Bigot W, Vanjak A, Burlacu R, Lopes A, Champion K, Depond A, Amador-Borrero B, Sene D, Comarmond C and Mouly S. Drug-drug interactions involving Dexamethasone in clinical practice: myth or reality? *J Clin Med* 2023; 12: 7120.

[11] Adly EM, Diab T and Hessien M. Dexamethasone-boosted mesenchymal stem cell secretome: insight into hepatic protection. *BMC Biotechnol* 2025; 25: 44.

[12] Ding Y, Zhao L, Mei H, Zhang SL, Huang ZH, Duan YY and Ye P. Exploration of Emodin to treat alpha-naphthylisothiocyanate-induced cholestatic hepatitis via anti-inflammatory pathway. *Eur J Pharmacol* 2008; 590: 377-386.

- [13] Lu L; Chinese Society of Hepatology and Chinese Medical Association. Guidelines for the management of cholestatic liver diseases (2021). *J Clin Transl Hepatol* 2022; 10: 757-769.
- [14] Chirag R and Arun Babu T. Successful treatment of prolonged cholestasis following hepatitis A infection in a child with oral steroid therapy. *BMJ Case Rep* 2023; 16: e257477.
- [15] Chawla RK, Bonkovsky HL and Galambos JT. Biochemistry and pharmacology of S-adenosyl-L-methionine and rationale for its use in liver disease. *Drugs* 1990; 40 Suppl 3: 98-110.
- [16] Gabbia D, Pozzo L, Zigiutto G, Roverso M, Sacchi D, Dalla Pozza A, Carrara M, Bogiatti S, Floreani A, Guido M and De Martin S. Dexamethasone counteracts hepatic inflammation and oxidative stress in cholestatic rats via CAR activation. *PLoS One* 2018; 13: e0204336.
- [17] Czock D, Keller F, Rasche FM and Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* 2005; 44: 61-98.
- [18] Masrour O, Rayer C, Giguette B, Uguen T, Morcet J, Jezequel C, Houssel-Debry P, Jegonday MA, Moirand R and Bardou-Jacquet E. Dexamethasone improves clinical and biological tolerance of transcatheter arterial chemoembolization for hepatocellular carcinoma. *Dig Liver Dis* 2025; 57: 738-743.
- [19] Elharabi Z, Saba J and Akin H. Navigating the latest hepatitis B virus reactivation guidelines. *Diseases* 2025; 13: 355.
- [20] Lashgari NA, Khayatan D, Roudsari NM, Momtaz S, Dehpour AR and Abdolghaffari AH. Therapeutic approaches for cholestatic liver diseases: the role of nitric oxide pathway. *Naunyn Schmiedeberg Arch Pharmacol* 2024; 397: 1433-1454.
- [21] Tiao MM, Lin TK, Chen JB, Liou CW, Wang PW, Huang CC, Chou YM, Huang YH and Chuang JH. Dexamethasone decreases cholestatic liver injury via inhibition of intrinsic pathway with simultaneous enhancement of mitochondrial biogenesis. *Steroids* 2011; 76: 660-666.
- [22] Gou XH, He XN, Jiang SS, Tao W and He CH. Effects of glucocorticoid receptor agonists on hyperalgesia of rats with neuropathic pain and its mechanisms. *Zhongguo Ying Yong Sheng Li Xue Za Zhi* 2022; 38: 470-474.
- [23] Xu Y, Chen J, Jiang W, Zhao Y, Yang C, Wu Y, Li Q and Zhu C. Multiplexing nanodrug ameliorates liver fibrosis via ROS elimination and inflammation suppression. *Small* 2022; 18: e2102848.
- [24] Xia C and Min J. Methionine-MAT2A-SAM axis controls lipid levels by regulating ACSL4. *Oncol Lett* 2025; 30: 551.
- [25] Xu Z, Cao X, Zhu Z, Lei J, Li L, Zhang X and Chai J. Tumor necrosis factor alpha-induced activation of SREBP2 promotes cholesterol biosynthesis in cholestasis. *Biochim Biophys Acta Mol Cell Biol Lipids* 2025; 1870: 159642.
- [26] Bae CS, Lee Y and Ahn T. Therapeutic treatments for diabetes mellitus-induced liver injury by regulating oxidative stress and inflammation. *Appl Microsc* 2023; 53: 4.
- [27] Poupon R. Liver alkaline phosphatase: a missing link between cholestasis and biliary inflammation. *Hepatology* 2015; 61: 2080-2090.
- [28] Luan X, Chen P, Li Y, Yuan X, Miao L, Zhang P, Cao Q, Song X and Di G. TNF-alpha/IL-1beta-licensed hADSCs alleviate cholestatic liver injury and fibrosis in mice via COX-2/PGE2 pathway. *Stem Cell Res Ther* 2023; 14: 100.