Original Article

Efficacy of ursodeoxycholic acid in nonalcoholic fatty liver disease: An updated meta-analysis of randomized controlled trials

Wenyue Zhang MD[1], Yao Tang MD[1], Juan Huang MD[1,2], Huaidong Hu PhD[2]

[1]*Department of Infectious Diseases, Institute for Viral Hepatitis, Key Laboratory of Molecular Biology for Infectious Diseases, Institute for Viral Hepatitis, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China*
[2]*Department of Clinical Nutrition, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China*

Background and Objectives: The role of ursodeoxycholic acid (UDCA) in Nonalcoholic fatty liver disease (NAFLD) is not well-defined. In this meta-analysis, we analyzed the efficacy of UDCA for the treatment of NAFLD. **Methods and Study Design:** We searched the Web of Science, Pubmed, Embase and Cochrane library databases for relevant studies published before September 1, 2019. The randomized controlled trials (RCTs) that investigated the effectiveness of UDCA in NAFLD were selected and examined by Stata (version 12.0). **Results:** The forest plot displayed that UDCA treatment can significantly decrease the ALT (alanine aminotransferase) levels (p=0.007). Further, its' significant role in subgroup analyses (p=0.003 in people from Europe, p=0.001 in people older than 50 years and p=0.008 in longer duration). **Conclusions:** Although UDCA treatment was found beneficial in ALT-lowering, future meta-analysis will be required to fully confirm and validate the efficacy of UDCA in NAFL.

Key Words: ursodeoxycholic acid, nonalcoholic fatty liver, alanine aminotransferase, meta-analysis, randomized controlled trial

INTRODUCTION

Along with the increased incidence of obesity and other metabolic diseases, nonalcoholic fatty liver diseases (NAFLD) became more prevalent.[1,2] According to the histopathological findings, NAFLD can be subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH).[3] NAFL patients are presented with hepatic steatosis without hepatocyte ballooning injury; while, NASH patients are presented with hepatic steatosis as well as hepatocyte inflammation with or without liver fibrosis.[4] Accumulating evidence suggested that NAFLD patients have a considerable risk for developing hepatocellular carcinoma even in the absence of liver cirrhosis.[5,6] In addition, complications resulting from NAFLD are expected to be one of the leading reasons for liver transplantation.[7] Therefore, developing strategies that can aid in the prevention of NAFLD as well as new treatments are a major priority in the field of healthcare research.[8] In the past decades, ursodeoxycholic acid (UDCA) has gained attention for its hepatoprotective effects in liver diseases as well as in NAFLD.[9] UDCA constitutes 3% of total bile acids in the human body.[10] In NAFLD patients, Troisi et al demonstrated that treatment with UDCA for 3 months improved the liver enzymes, liver ultrasound image as well as glycemic control and insulin sensitivity.[11] However, several reports suggested that the beneficial impact of UDCA can be influenced by the patient's own bile acid metabolism.[12,13] Numerous recent randomized controlled trials (RCTs) have emerged to verify the role of UDCA in NAFLD. Therefore, in this meta-analysis, we aim to present an updated and sensitive qualitative and quantitative analysis for all relevant RCTs.[14,15] To this end, we gathered all the relevant RCTs and conducted rigorous evaluation to investigate the utility of UDCA in NAFLD in terms of population, age and treatment duration.

METHODS

Literature search

We searched the Web of Science, Pubmed, Embase and Cochrane library databases as well as Chinese articles for RCTs published before September 1, 2019.[16,17] We used the medical Subject Heading (MeSH) terms and comparable terms in the related databases to screen out articles.

Corresponding Author: Huaidong Hu, Department of Clinical Nutrition, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China.
Tel: +18953231126
Email: huhuaidong@cqmu.edu.cn
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The key search terms included: (Acid, Ursodeoxycholic OR Ursacholic Acid OR 3 alpha,7 beta-Dihydroxy-5 beta-cholan-24-oic Acid OR Deoxyursocholic Acid OR Ursolvan OR Delursan OR Destolit OR Sodium Ursodeoxycholate OR Cholofalk OR Ursofalk OR Urso Heumann) AND (Nonalcoholic Fatty Liver Disease OR NAFLD OR Nonalcoholic Steatohepatitis OR Livers, Nonalcoholic Fatty OR Steatohepatitides, Nonalcoholic) AND (Randomized OR Randomized controlled trial).

Inclusion and exclusion criteria

The following inclusion criteria were applied in this study: (1) Only RCTs were included; (2) The intervention group received either UDCA alone or UDCA composite;[18] (3) The control group patients did not receive UDCA; (4) All RCTs participants should be adults with confirmed NAFLD diagnosis;[19] (5) Comparisons between the experimental and control groups should be presented in the form of mean±standard deviation (SD) or mean±standard error (SE). On the other hand, studies were be excluded in the following cases: (1) Studies involving pregnant patients or patients younger than 18 years old; (2) Studies with vague or missing outcomes that could not be resolved via email communications; (3) Studies without control group; (4) Studies in which UDCA was combined with other drugs; (5) If the duration of UDCA treatment was less than 8 weeks.

Data extraction

Two investigators (ZWY and HDH) screened the titles and abstracts of all retrieved articles independently. The following data were extracted: design of each study, patient characteristics, number of participants, properties of the study population, geographical location, duration of intervention, year of publication, and mean±SD (or mean±SE). In order to minimize the relative heterogeneity, we consider that the duration of intervention to be from baseline till the end of trial (at least 8 weeks). In the case of insufficient or vague data, the corresponding authors were contacted by email twice before excluding the study.

Evaluation of bias

The risk of bias among the selected trials was evaluated according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions as described previously.[20] The quality of each trial was assessed in the following 6 aspects: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Assessment results were presented as one of three categories: low, unclear or high risk of bias.

Statistical analysis

We used Stata version 12.0 (Stata Corporation, College Station, TX, USA) for analyzing continuous variables in this study. We used data presented in the form of mean±SD. Data presented as mean±SE were converted to SD using the following formula: mean = mean (after treatment) – mean (baseline); SD = SE × square root n (n: number of participants) and SD = square root [(SD baseline)^2 + (SD after-treatment)^2 - (2R × SD baseline × SD after-treatment)], the correlation coefficient (R)= 0.5.20 The results of the meta-analysis are displayed in the form of standardized mean difference (SMD) and 95% confidence interval (CI). Further, Chi-squared and I-square (I^2) tests were calculated to reveal the statistical heterogeneity among the analyzed trials. An I^2 <60% indicated moderate heterogeneity. We applied fixed-effect model for analysis; otherwise, the random-effect model was used as detailed previously.[21] SMD values close to 0 (p>0.05) indicated no statistical significance. In contrast, SMD was considered statistically significant when it was away from 0 (p<0.05). In order to explore the heterogeneity between studies, subgroup analyses were conducted by examining the geographical region, age and duration of intervention as detailed previously.[22,23]

RESULTS

Study features

We collected 134 articles from different data bases in the initial online search. After applying the different inclusion and exclusion criteria，at total of 11 full-text articles including systemic reviews were selected for further screening. Nevertheless, an additional 2 articles were excluded due to insufficient data. Finally, 9 RCTs with 1106 participants were included in this meta-analysis (Figure 1). In addition, pre- and post-treatment serum biochemical parameters are presented in supplementary file (supplementary file 1). Among the enrolled RCTs, two trials were conducted in China,[16,17] one in Korea,[18] one in Italy,[24] another in Germany,[25] one in Brazil,[26] one in the United States,[27] another in Turkey[28] and finally one study was conducted in France.[29] The duration of intervention ranged from 8 weeks to 24 weeks, and the common form intake of UDCA was through oral administration. The basic characters for the involved trials are summarized shown in Table 1.

Quality assessment

We evaluated the quality of the included studies by the Cochrane Collaboration's tool.[20] Owing to the different study qualities, the evaluation of each parameter was also unequal. In the random sequence generation, 3 trials demonstrated unclear risk of bias.[16,17,26] A total of 6 trials were at low risk of bias in the Blinding factor[18,24-27,29] while the other three studies had unclear risk. For the incomplete outcome data and selective reporting, all 9 trials were at low risk of bias.[16-18,24-29] In addition, 4 trials were ranked unclear risk of bias in the allocation concealment and free of other biases parameters (Table 2).

Meta-analysis

Compared to the control group (n=497), our meta-analysis indicated a significant benefit for the use of UDCA in decreasing the serum alanine aminotransferase (ALT) levels in the intervention group (n=403; SMD=-0.18 at 95% CI [-0.32 to -0.05], p=0.007, I^2=50.7%) with inconspicuous heterogeneity. On the other hand, UDCA treatment did not cause a statistically significant reduction in the aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) levels (SMD=-0.08, 95% CI [-0.22 to 0.05], p=0.223 and -0.15, 95% CI [-0.45 to 0.14], p=0.305, respectively; Figure 2-4). Similarly, its

Table 1. Basic characteristics of involved trials

Author, year	Country	Participant number	Completed number (inter/cont)	Intervention	Dosage	Age	Duration	Diagnosis	Main outcomes measure
Oh B, 2016[18]	Korea	168	152 (78/74)	URSA-S	50 mg/d	43.63	8 weeks	NAFLD	ALT, AST, GGT, total bilirubin
Gianturco V, 2013[24]	Italy	200	196 (46/46)	UDCA	300 mg/d	62	12 months	NAFLD	ALT, AST, GGT, albumin
Santos VN, 2003[26]	Brazil	30	28 (14/14)	UDCA	10 mg/kg/d	38.4	3 months	NAFLD	ALT
Leuschner UF, 2010[25]	Germany	185	160 (78/82)	UDCA	23-28 mg/kg/d	41.45	18 months	NAFLD	ALT, AST, GGT, AP, total bilirubin, albumin
Lindor KD, 2004[27]	America	166	121 (56/65)	UDCA	13-15 mg/kg/d	45.4	2 years	NAFLD	ALT, AST, GGT, AP, total bilirubin, albumin
Kiyici M, 2003[28]	Turkey	44	44 (17/27)	UDCA	13-15 mg/kg/d	48.9	6 months	NAFLD	ALT, AST, GGT, AP
Guang JI, 2008[16]	China	135	135 (33/102)	UDCA	750 mg/d	44.43	24 weeks	NAFLD	ALT, AST, GGT
Hong Q, 2007[17]	China	52	52 (26/26)	UDCA	45-60 mg/kg/d	51.8	6 months	NAFLD	ALT, AST, GGT
Ratziu V, 2011[29]	France	126	116 (55/61)	UDCA	28-35 mg/kg/d	49.8	12 months	NAFLD	ALT, AST, GGT

URSA-S: ursodeoxycholic acid composite; UDCA: ursodeoxycholic acid; NAFLD: nonalcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: γ-glutamyl transpeptadase; AP: alkaline phosphatase.

Table 2. Risk of bias

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Free of other bias
Oh B et al., 2016[18]	L	L	L	L	L	L
Gianturco V et al, 2013[24]	L	L	L	L	L	U
Santos VN et al, 2003[26]	U	U	L	L	L	U
Leuschner UF et al, 2010[25]	L	L	L	L	L	L
Lindor KD et al, 2004[27]	L	U	L	L	L	L
Kiyici M et al, 2003[28]	L	L	U	L	L	U
Guang JI et al, 2008[16]	U	L	U	L	L	L
Hong Q et al, 2007[17]	U	U	U	L	L	L
Ratziu V et al, 2010[29]	L	U	L	L	L	U

L: low risk of bias; H: high risk of bias; U: unclear.

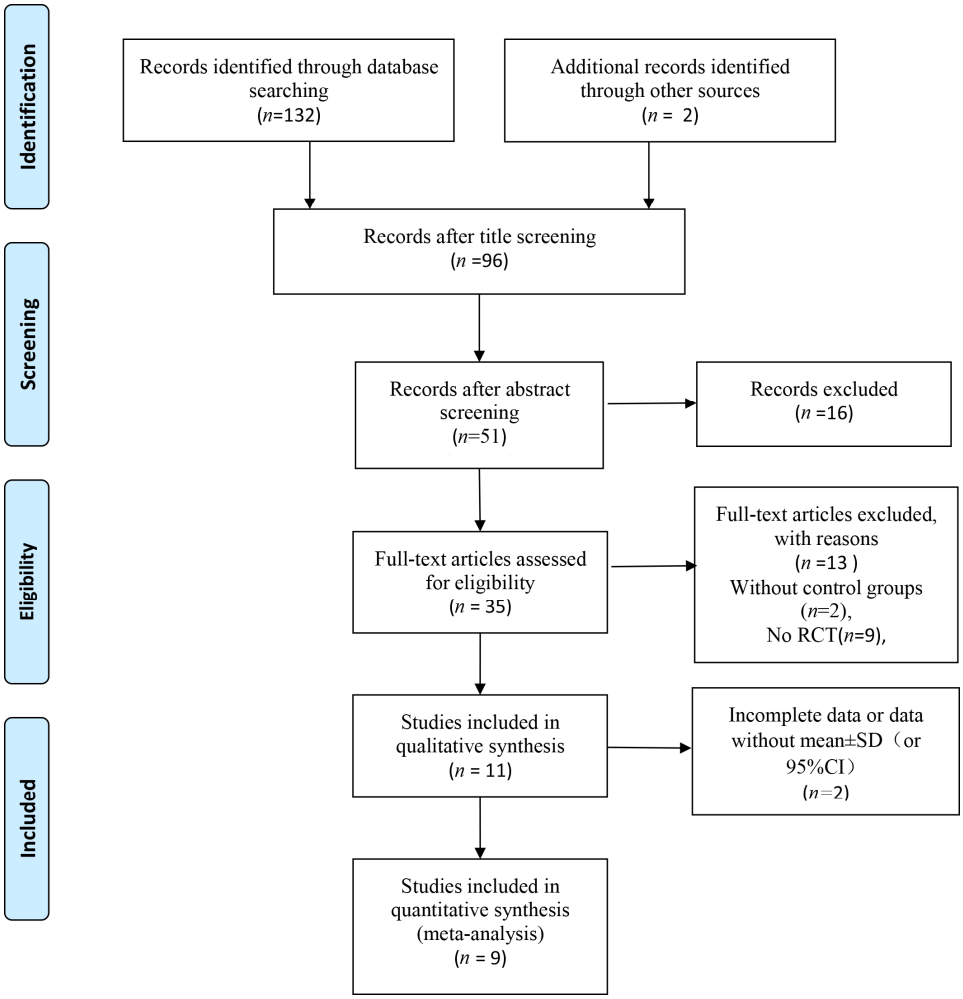

Figure 1. PRISMA flow diagram representing the different phases of this study.

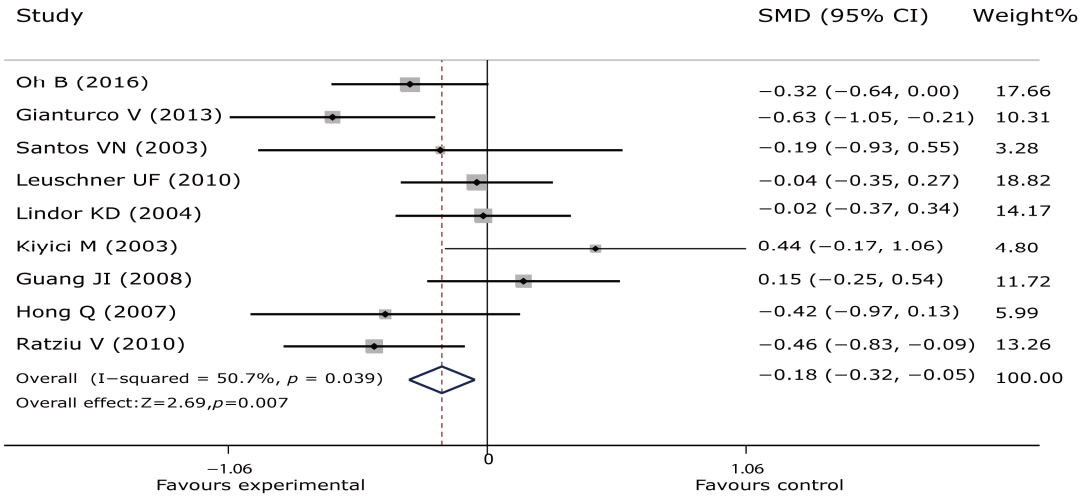

Figure 2. Forest plot of the meta-analysis for comparing experimental with control groups in ALT.

impact on the alkaline phosphatase (AP), total bilirubin and albumin in the experimental groups was not significant too (SMD=-0.03, 95% CI [-0.25 to 0.19], p=0.774; 0.02, 95% CI [-0.16 to 0.21], p=0.804; and 0.05, 95% CI [-0.16 to 0.25], p=0.66, respectively). Figure 5-7.

Subgroup analyses

Next, we carried out subgroup analyses among different subsets: duration of intervention (≤6 months and >6 months), participants' age (≤50 years and >50 years) and geographical region (Asia, Europe and America) (Supplementary file 2). Participants from Brazil (South America)[26] and The United States (North America)[27] were categorized into America. Regarding the duration of intervention, our results indicated that longer UDCA treatment duration (>6 months) significantly decreased the ALT levels (SMD=-0.24, 95% CI [-0.42 to -0.06], p=0.008). However, it did not affect the remaining indices. Similar-

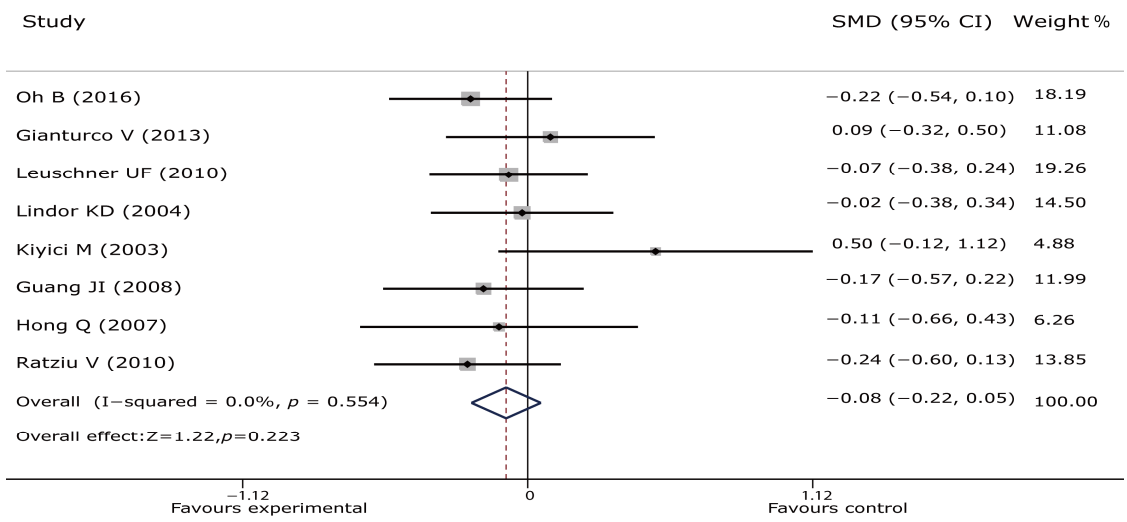

Figure 3. Forest plot of the meta-analysis for comparing experimental with control groups in AST.

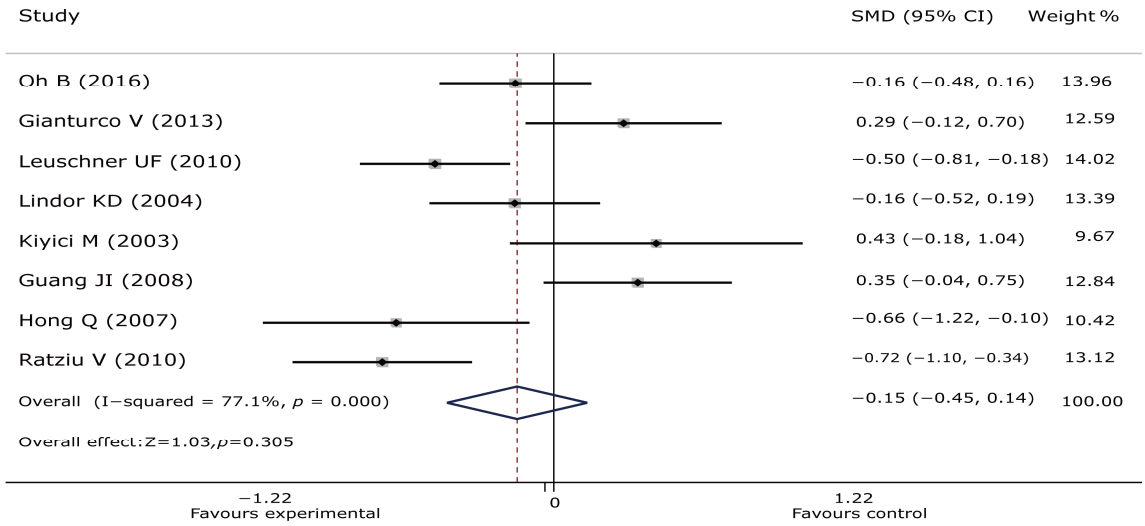

Figure 4. Forest plot of the meta-analysis for comparing experimental with control groups in GGT.

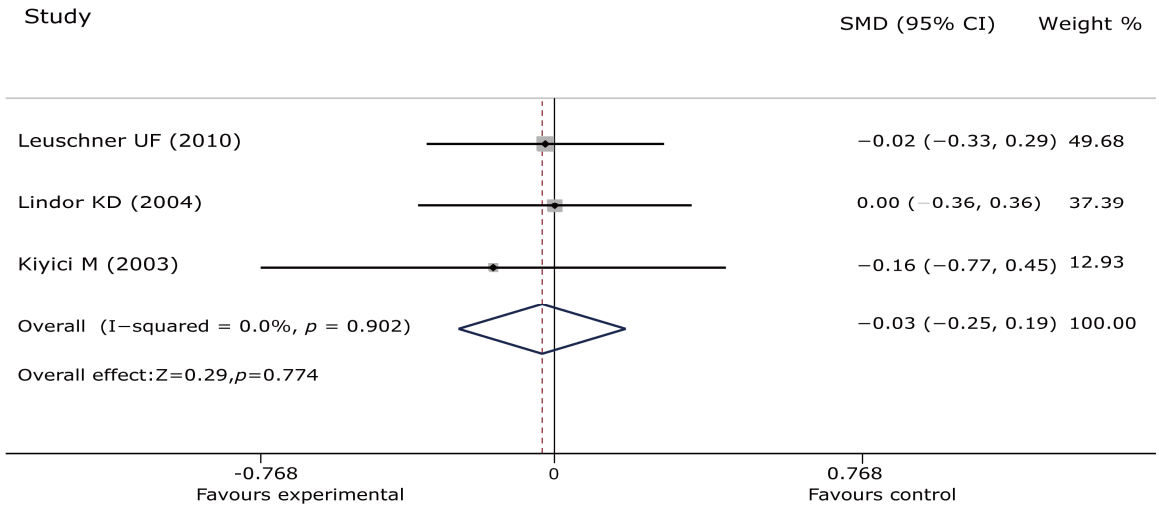

Figure 5. Forest plot of the meta-analysis for comparing experimental with control groups in AP.

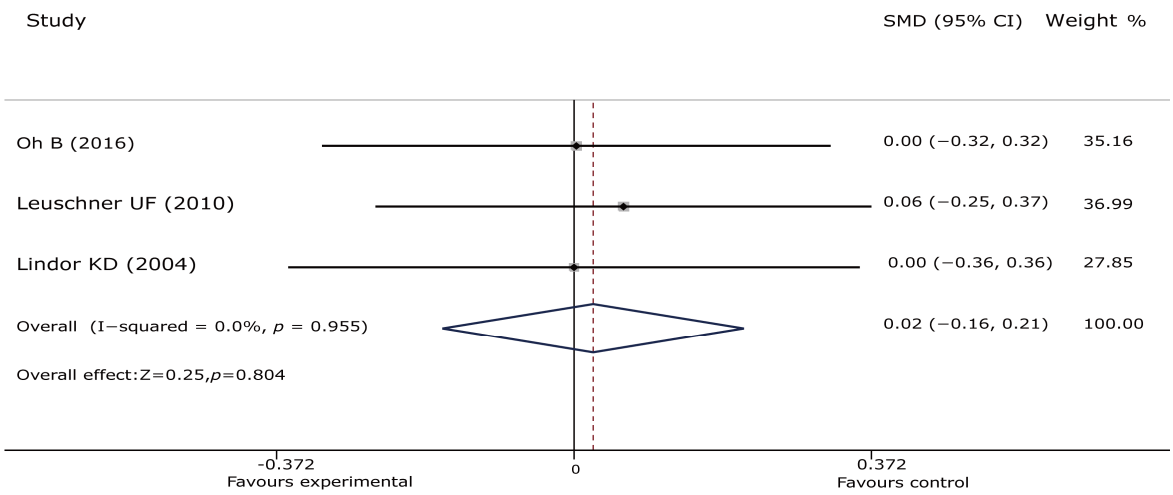

Figure 6. Forest plot of the meta-analysis for comparing experimental with control groups in total bilirubin

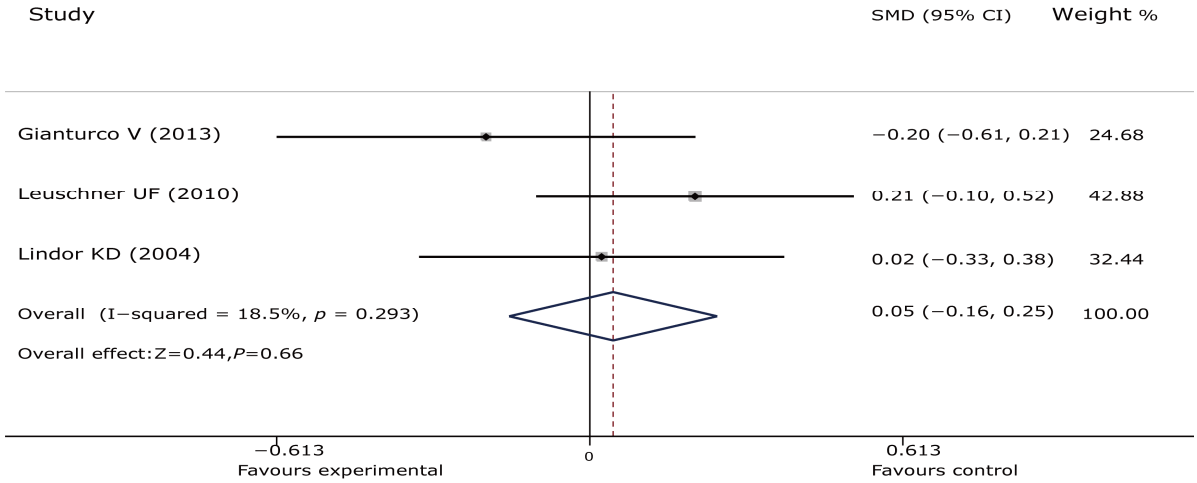

Figure 7. Forest plot of the meta-analysis for comparing experimental with control groups in albumin.

ly, patients older than 50 years demonstrated a significant decrease in ALT levels following UDCA administration (SMD=-0.55, 95% CI [-0.89 to -0.22], p=0.001). The change in ALT levels was not significant among Asian and American populations (SMD=-0.1, 95% CI [-0.32 to 0.11] and -0.05, 95% CI [-0.37 to 0.27], respectively). Interestingly, following UDCA treatment, the change in ALT levels was significant in the European population (SMD=-0.32, 95% CI [-0.52 to -0.11], p=0.003).

DISCUSSION

NAFLD is a chronic liver disorder that affects about 24% of the adult population worldwide.[30] Therefore, we aimed to analyse and determine the beneficial impact of UDCA treatment among NAFLD patients. In this updated meta-analysis, our results indicated the UDCA treatment can significantly decrease the ALT levels. Further, the subgroup analyses suggested the significant role of UDCA treatment in different geographical regions, age groups and treatment duration. Common complications of NAFLD include type 2 diabetes, cardio-vascular disease and chronic kidney diseases.[31] Those complications often result in the development of other chronic conditions thereby, ultimately impacting the patients' quality of life.[32] Mazzella et al previously demonstrated that UDCA was more efficient than chenodeoxycholic acid in promoting weight loss.[33] Moreover, its hepatoprotective impact in cholestasis was established and it was attributed to its ability to expel hydrophobic and toxic bile acids.[34] Nevertheless, exploring the applicability of UDCA treatment in hepatobiliary diseases will be instrumental.

In this meta-analysis, we analyzed the impact of UDCA treatment on ALT, AST, GGT, AP, bilirubin and total albumin levels. ALT and AST are liver enzymes that can reflect liver injury or inflammation.[35] GGT is presents in the liver and biliary epithelial cells and it is sensitive marker to hepatobiliary diseases; while, AP levels reflect liver diseases or bones growth issues.[36] Bilirubin is formed by hemoglobin breakdown and high bilirubin concentration often reflects hepatocyte damage thereby causing jaundice. Albumin is made by the liver cells and alteration in albumin levels is an established clinical indication of chronic liver disease.[37-39] Following UDCA administration, significant changes were observed in ALT levels and its subgroups, but changes in the remaining serum biochemical parameters were not significant. This could be possibly attributed to the insufficient number of patients or analyzed parameters among the RCTs. For

instance, only 3 trials analyzed the AP,[25,27,28] albumin[24,25,27] and bilirubin[18,25,27] levels, respectively. Therefore, analyzing future studies will be required to confirm our current observations.

In this meta-analysis, trials were selected from online databases and previously published systemic reviews.[14,15] From Orlando et al's review,[14] we selected only two RCTs due to insufficient data in the other studies.[26,27,40,41] Among the 12 clinical trials analyzed by Xiang et al,[15] we were able to extract data from 5 clinical trials only[17,25,27-29,42-48] due to the restriction of our inclusion criteria. Therefore, this study analyzed 7 RCTs[16,17,25-29] from the previously published systemic reviews in addition to 2 newly published articles.[18,24] We noticed that the application of dosage and the period may have something to do with the outcomes. Among the included trials, the studies of Hong Qian[17] and Ratiz V[29] applied UDCA with a relatively large dosage and a relatively long application duration, which contributed to the statistical significance of the forest plots in ALT, AST and GGT. The subgroup analysis cannot be performed due to the dosage and duration of UDCA varied among the included studies as well as the methods used for evaluation of the final results. Therefore, the studies with more complete dosage gradient and time gradient designs are needed to explore whether the high dosage and long duration can help improve the treatment effect.

Ingestion of UDCA was shown to be associated with gastrointestinal adverse effects like diarrhea in three clinical trials.[25] Nevertheless, the other RCTs did not report serious adverse reactions and no significant difference was observed between the UDCA group and the control group. The impact of UDCA on the histological picture was analyzed in few clinical trials; however, we found it difficult to conduct a meta-analysis on the histological findings with a small number of clinical trials.[24-28] Similarly, the small number of enrolled trials hindered our efforts to analyze the publication bias by Funnel plots, Egger's test or Begg's test. Therefore, future meta-analysis will be required to analyze the impact of UDCA with respect to the abovementioned aspects. Reardon, J et al.[49] did not only report NAFLD in UDCA treatment, but also include alcoholic liver disease (ALD), autoimmune hepatitis (AIH), liver transplant and viral hepatitis, which were demonstrated in the form of table. However, in this study, we only explored the beneficial impact of UDCA administration in NAFLD in order to get rid of bias among other liver diseases. Moreover, our data were conducted by meta-analysis and subgroup analyses, then showed in the form of forest plot and table. To sum up, our results indicated the UDCA treatment can significantly decrease the ALT levels. Aside from the limited number of included studies, this meta-analysis suffered from several limitations. First, complications resulting from NAFLD could interfere with the effects of UDCA. Additionally, all enrolled patients were diagnosed with NAFLD without differentiating between NAFL or NASH patients, which could be a possible source of data bias. Most enrolled studies applied double-blinding, but the details of randomizations were unclear, which contributed the incomplete assessment. Finally, 2 trials were published in non SCI journals which may affect the overall study analysis.[16,17]

Conclusion

In conclusion, our results demonstrate the UDCA was indeed beneficial in lowering the ALT levels among NAFLD patients which promotes the disease recovery. To the best of our knowledge, the impact of UDCA on ALT was not previously published by other meta-analyses. However, more studies are required to thoroughly verify the role of UDCA on the AST, GGT, AP, total bilirubin and albumin levels. Also, the impact of UDCA dosage on chronic liver diseases should be conducted in future studies.

AUTHOR DISCLOSURES

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Supplementary table 1. Serum biochemical parameters in pre- and post-treatment.

Study	Outcome	Unit	Experimental		Control		SMD
			Before	After	Before	After	
Oh B et al	ALT	IU/L	49.4±35.2	39.4±26.0	49.2±26.7	48.4±26.0	-0.32
	AST	IU/L	33.0±16.7	29.2±36.2	32.3±10.4	35.6±36.0	-0.22
	GGT	IU/L	51.8±40.5	45.5±22.2	57.9±45.4	57.6±22.0	-0.16
	Total bilirubin	mg/dL	0.86±0.39	0.84±0.35	0.83±0.25	0.80±0.34	0
Gianturco V et al	ALT	IU/L	54.0±4.90	51.8±3.30	52.5±3.90	52.9±3.90	-0.63
	AST	IU/L	49.0±2.90	48.9±3.50	50.0±3.70	49.6±3.30	0.09
	GGT	IU/L	58.9±5.10	59.4±3.70	60.5±4.70	59.7±3.80	0.29
	Albumin	g/dL	3.70±0.90	3.70±0.90	3.50±0.10	3.63±0.10	-0.20
Santos VN et al	ALT	IU/L	81.2±37.6	52.2±24.4	66.4±38.0	43.7±19.4	-0.19
	ALT	IU/L	100±53.0	59.6±58.4	109±58.1	71.4±62.6	-0.14
	AST	IU/L	58.9±30.3	42.4±30.8	61.0±25.3	46.7±28.8	-0.07
Leuschner UF et al	Total bilirubin	umol/L	11.9±5.78	12.0±0.89	11.4±7.48	11.1±0.91	0.06
	AP	U/L	165±48.3	154±47.6	173±45.0	164±43.9	-0.02
	GGT	U/L	84.8±71.7	32.3±64.2	90.9±84.7	74.1±54.0	-0.50
	Albumin	g/L	46.4±4.33	46.6±3.62	46.6±4.37	46.0±4.26	0.21
Lindor KD et al	ALT	IU/L	105±56.3	71.9±69.8	108±73.4	76.4±67.3	-0.02
	AST	IU/L	71.4±42.4	49.7±53.2	70.6±41.4	49.9±43.8	-0.02
	GGT	IU/L	101±113	59.1±117	109±99.1	83.9±46.3	-0.16
	AP	U/L	155±103	147±54.2	154±103	146±47.5	0
	Total bilirubin	mg/dL	0.80±0.50	0.80±0.30	0.90±0.70	0.90±0.60	0
	Albumin	g/dL	4.40±0.40	4.30±0.40	4.30±0.50	4.10±0.40	0.02
Kiyici M et al	ALT	IU/L	76.0±27.2	55.1±29.7	81.8±46.2	44.8±29.6	0.44
	AST	IU/L	47.5±20.6	43.7±17.7	45.4±20.8	32.1±15.6	0.50
	AP	U/L	89.6±36.7	94.3±30.5	98.7±34.3	109±36.9	-0.16
	GGT	U/L	47.8±28.4	32.2±12.4	64.2±49.4	32.7±21.3	0.43
Guang JI et al	ALT	U/L	74.1±39.2	48.7±25.2	71.2±41.0	40.5±21.3	0.15
	AST	U/L	61.8±26.1	33.9±16.4	55.3±23.9	31.2±11.9	-0.17
	GGT	U/L	81.2±46.8	56.1±38.4	86.4±48.0	46.5±27.7	0.35
Hong Q et al	ALT	U/L	110±25.0	45.0±20.0	106±22.0	50.0±18.0	-0.42
	AST	U/L	100±20.0	38.0±15.0	42.0±18.0	102±17.0	-0.11
	GGT	U/L	85.0±26.0	40.0±18.0	78.0±24.0	48.0±20.0	-0.66
Ratziu V et al	ALT	IU/L	109±70.0	78.5±55.0	103±69.0	101±35.0	-0.46
	AST	IU/L	61.0±31.0	56.1±59.0	59.0±31.0	64.3±37.0	-0.24
	GGT	IU/L	122±148	59.8±28.0	126±118	150±48.0	-0.72

Data are shown as mean±SD.
ALT: Alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; AP: Alkaline phosphatase.

Supplementary table 2. The outcomes of subgroup analyses.

Variables	Duration		Age		Region		
	≤6 months	> 6months	≤50 years	> 50 years	Asia	Europe	America
ALT							
SMD	-0.11	-0.24	-0.11	-0.55	-0.1	-0.32	-0.05
95%CI	-0.32, 0.09	-0.42, -0.06	-0.26, 0.03	-0.89, -0.22	-0.32, 0.11	-0.52, -0.11	-0.37, 0.27
p value	0.285	0.008	0.131	0.001	0.333	0.003	0.765
I^2	47.10%	61.50%	41.70%	0	60.10%	65.20%	0
p - heterogeneity	0.109	0.051	0.113	0.542	0.057	0.056	0.677
AST							
SMD	-0.11	-0.07	-0.11	0.02	-0.11	-0.08	-0.02
95%CI	-0.32, 0.1	-0.25, 0.11	-0.26, 0.04	-0.31, 0.34	-0.32, 0.1	-0.29, 0.12	-0.38, 0.34
p value	0.323	0.447	0.166	0.922	0.323	0.42	0.904
I^2	31.30%	0	2.0%	0	31.30%	0	....
p - heterogeneity	0.225	0.695	0.403	0.562	0.225	0.507	....
GGT							
SMD	-0.01	-0.28	-0.16	-0.16	-0.01	-0.32	-0.16
95%CI	-0.45, 0.43	-0.68, 0.12	-0.49, 0.17	-1.10, 0.77	-0.45, 0.43	-0.87, 0.24	-0.52, 0.19
p value	0.964	0.172	0.339	0.73	0.964	0.265	0.369
I^2	73.40%	79.80%	77.60%	86.20%	73.40%	85.70%	....
p - heterogeneity	0.01	0.002	0	0.007	0.01	0.001	....
AP							
SMD	-0.16	-0.01	-0.03	....	-0.16	-0.02	0
95%CI	-0.77, 0.45	-0.25, 0.22	-0.25, 0.19	....	-0.77, 0.45	-0.33, 0.29	-0.36, 0.36
p value	0.606	0.913	0.774	....	0.606	0.881	0.995
I^2	....	0	0	....	....	....	....
p - heterogeneity	....	0.918	0.902	....	....	....	....
Albumin							
SMD	....	0.05	0.13	-0.2	....	0.06	0.02
95%CI	....	-0.16, 0.25	-0.11, 0.36	-0.61, 0.21	....	-0.19, 0.3	-0.33, 0,38
p value	....	0.66	0.288	0.331	....	0.654	0.899
I^2	....	18.50%	0	....	....	58.80%	....
p - heterogeneity	....	0.293	0.449	....	....	0.119	....
Total bilirubin							
SMD	0	0.04	0.02	....	0	0.06	0
95%CI	-0.32, 0.32	-0.2, 0.27	-0.16, 0.21	....	-0.32, 0.32	-0.25, 0.37	-0.36, 0.36
p value	0.986	0.768	0.804	....	0.986	0.696	1
I^2	....	0	0	....	....	....	....
p - heterogeneity	....	0.789	0.955	....	....	....	....

Data are shown as mean±SD.
ALT: Alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; AP: Alkaline phosphatase.