Systematic Review and Meta-Analysis

Medicine®

OPEN

Glucocorticoid versus traditional therapy for hepatitis B virus-related acute-on-chronic liver failure

A systematic review and meta-analysis

Ranran Gao, MM[a], Yang Li, MM[b], Yang Cao, MM[a], Rongjiong Zheng, MM[a], Li Tang, MM[a], Jianzhong Yang, MM[a], Xiaobo Lu, PhD[c,*]

Abstract

Objective: This meta-analysis aimed to assess the efficacy and safety of glucocorticoid versus traditional therapy for hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF).

Methods: PubMed, Cochrane Central Register of Clinical Trials, and EMBASE were searched. All clinical studies, including randomized controlled studies and cohort studies, comparing glucocorticoids with traditional treatments (until November 1, 2018), were included.

Results: A total of 3 randomized controlled trials and 5 cohort studies (including 3 retrospective cohort studies), involving 538 patients, were subjected to the meta-analysis. The total bilirubin levels before treatment were not significantly different (odds ratio [OR]: −0.97; 95% confidence interval [CI]: −2.56 to 0.62; $P = .23$), and, however, they were significantly reduced after treatment in the corticosteroid group compared with the traditional treatment group (OR: −8.83; 95% CI: −14.99 to 2.67; $P = .005$). Moreover, prothrombin time was significantly long before treatment in either group, with no significant differences (OR: 0.28; 95% CI: −0.79 to 1.34; $P = 0.61$). However, after treatment, prothrombin time was significantly shortened in the traditional treatment group (OR: 31.71; 95% CI: 3.62–59.81; $P = .03$). Furthermore, inpatient mortality (OR: 0.23; 95% CI: 0.08–0.67; $P = .007$) and ascites events (OR: 0.35; 95% CI: 0.18–0.67; $P = .90$) were significantly lower in the corticosteroid treatment group.

Conclusions: Glucocorticoid is more effective for reducing the T-bili level, significantly decreasing in-hospital mortality and ascites events in HBV-related ACLF patients. Moreover, bilirubin may play a pivotal role in the early stage of HBV-related ACLF progression to advanced liver failure.

Abbreviations: ACLF = acute-on-chronic liver failure, ALF = acute liver failure, ALT = alanine aminotransferase, HBV = hepatitis B virus, PT = prothrombin time, RCT = randomized controlled trial, T-bili = total bilirubin.

Keywords: Glucocorticoid, hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF), meta-analysis, systematic review

1. Introduction

The main manifestations of liver failure include acute-on-chronic liver failure (ACLF), acute liver failure, and end-stage liver disease.[1] Because of the inconsistencies in the Eastern and Western academic definitions of the ACLF pathological process, understanding and performance in the treatment of ACLF are controversial. In the pathological process of ACLF, chronic hepatitis has been emphasized in Eastern regions, whereas

Editor: Sherief Abd-Elsalam.

RG and YL contributed equally to this study.

This work was supported by the National Science and Technology Projects of China (NSTP; No. 2018ZX10302206-004-011 and No. 2018ZX10302206-002-010), and the NNSF of China (No. 81260246 and No. 81660333).

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of First Aid Trauma Center, [b] Department of Cardiology, [c] Infectious Disease Center, the First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, China.

[*] Correspondence: Xiaobo Lu, Infectious Disease Center, the First Affiliated Hospital of Xinjiang Medical University, No. 137, Liyushan South Road, Urumqi 830054, Xinjiang, China (e-mail: xjykdluxiaobo@126.com).

How to cite this article: Gao R, Li Y, Cao Y, Zheng R, Tang L, Yang J, Lu X. Glucocorticoid versus traditional therapy for hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF): a systematic review and meta-analysis. Medicine 2020;99:25(e20604).

Received: 4 December 2019 / Received in final form: 14 April 2020 / Accepted: 6 May 2020

http://dx.doi.org/10.1097/MD.0000000000020604

cirrhosis has been emphasized in Western regions.[2,3] However, the core acute insulting factors in ACLF include alcohol, viral hepatitis, and autoimmune liver diseases, which would lead to liver systemic inflammation of the liver based on chronic hepatitis/cirrhosis, further resulting in multiple organ dysfunctions and a short-term mortality >50%.[4]

Liver transplantation is the first choice in the treatment of ACLF. Due to lacking the hepatogenic agents, the active identification and mitigation of acute insults, followed by emergency care and supportive treatment, are essential. It has been shown that steroid administration for severe alcoholic hepatitis and fulminant autoimmune hepatitis can improve transplant-free survival.[5] The immunosuppressive effects of glucocorticoid may enhance hepatitis B virus (HBV) replication and aggravate the HBV infection. For these reasons, glucocorticoid has not been widely used in the treatment of HBV-related ACLF.

In recent years, glucocorticoid treatment for HBV-related ACLF has been considered safer, due to the generation of nucleoside analogues and effective infection control measures. Studies have shown that early glucocorticoid treatment for severe hepatitis can prevent the hepatic cell necrosis and provide the possibility of liver regeneration.[6–8] However, whether glucocorticoid therapy is effective for HBV-related ACLF remains controversial. In this meta-analysis, the efficacy and safety of glucocorticoid therapy in the treatment of HBV-related ACLF were investigated, in comparison to traditional drug support therapies.

2. Methods

2.1. Literature search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline,[9] and an unpublished protocol on September 29, 2018 (S1 file and S1 appendix), were followed. The PubMed, Cochrane Library Central Register of Controlled Trials (CENTRAL), and EMBASE were searched, to obtain relevant studies until November 1, 2018. The following search terms and key words were used: "acute-on-chronic liver failure," "hepatitis B virus," and "glucocorticoid." The reference lists of the identified reports were also checked. This study protocol was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Xinjiang Medical University and conformed to the principles and guidelines of the Declaration of Helsinki.

2.2. Study selection

Study eligibility was independently assessed by 2 investigators (RRG and YL). Inclusion criteria were as follows: any randomized controlled trial (RCT) or observational cohort study that compared the outcomes of ACLF patients between glucocorticoid treatment and control groups; the ACLF population included in the study was all related to HBV infection; ACLF patients were diagnosed based on the APASL criteria; the studies were published in peer-review journals; and the included studies had obtained informed consent from patients. Exclusion criteria were as follows: patients with alcoholic liver disease, autoimmune liver disease, primary biliary sclerosis, liver degeneration, hemochromatosis, or other non-severe hepatitis caused by hepatitis viruses; studies without definite indicators for outcome assessment after glucocorticoid therapy; patients with cancer, serious immune system disease, or blood diseases; studies lacking control groups; systemic reviews and meta-analyses; full text not available; and studies not concerning human.

2.3. Definition of clinical outcomes

Based on the included studies, primary endpoints included in-hospital death, bleeding events, and liver function indexes. In-hospital death referred to the deaths of HBV-related ACLF patients due to liver failure during hospital treatment. The bleeding events referred to gastrointestinal bleeding, bleeding at the injection site, and subcutaneous hemorrhage. The main indexes of liver function included the alanine aminotransferase (ALT) level, prothrombin time (PT), total bilirubin (T-bili) level, and HBV-DNA replication. Secondary endpoints included the ascites and hospitalization duration. Ascites was mainly caused by hypoproteinemia during liver failure deterioration. Hospitalization duration referred to the period from admission to hospital to discharge or death.

2.4. Data extraction and assessment

Data were extracted from the included studies by 2 independent investigators (JZY and LT) to build a database, following a standardized procedure, which included the baseline characteristics and endpoints. For the measured outcomes, all endpoints were extracted from each study and classified. The risk of bias was evaluated independently by two investigators (YL and RJZ), based on the Cochrane Collaboration guidelines.[10] In situations of disagreement, a third investigator (YC) was involved for judgment.

2.5. Statistical analysis

The RevMan 5.3 software (the Cochrane Collaboration) was used for statistical analysis. We used odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to estimate the effectiveness of different outcomes.[11] We used Higgins's and Thompson's I^2 statistics to evaluate the statistical heterogeneity between studies.[12] Fixed-effect models (Mantel-Haenszel method) were used when there was no significant statistical heterogeneity,[13] otherwise we used the random-effect models.[14] When zero events occurred in one of the treatment groups, 0.5 was added to each cell of the 2×2 table to evaluate the treatment effectiveness. The funnel plots, Begg and Egger tests were used to evaluate the publication bias.[15,16] The sensitivity analysis was tested by excluding one trial at each time.

3. Results

3.1. Search results and study characterization

Among a total of 1194 potentially eligible studies, after title and abstract screening, 8 initially identified trials involving 538 patients fulfilled the inclusion criteria and were included in the meta-analysis analysis. The flow diagram is shown in Supple. Fig. 1, http://links.lww.com/MD/E341.[17–24] A total of 3 RCTs and 5 cohort studies were analyzed, 3 of which were retrospective cohort studies. Among these studies, 247 patients received the corticosteroid therapy regimen, and 291 patients received traditional treatment, with or without placebo treatment. The follow-up period ranged from 2 to 104 weeks. The ages ranged from 31 to 50 years. Male percentages in the corticosteroid therapy regimen group ranged from 25.6% to 94.4%, and from 18.2% to 89.5% in the control group. In the glucocorticoid treatment groups, 3 studies only used prednisone, 3 only used dexamethasone, 1 only used methylprednisolone, and 1 used either methylprednisolone or prednisone (Table 1).

Table 1

Baseline characteristics of the included trials.

Trial[17–24]	Enrolling period	Follow-up, wek	Inclusion criteria	Corticosteroid group, patient number	Corticosteroid therapy regimen	Regular therapeutic group, patient number	Age, years (Case group vs control group)	Study characteristics	Liver biopsy	Country
Fujiwara et al[19]	1994–2004	4	The diagnosis of chronic hepatitis B viral carriers was made, based on either the positivity of hepatitis B surface antigen for at least 6 mo before entry, or the positivity of hepatitis B surface antigen, antihepatitis B core antibody at high titer and negativity or low titer of IgM anti-hepatitis B core antibody in patients with follow-up periods <6 mo before admission. The patients, fulfiling the following 3 criteria during the course, were defined as severe exacerbation: PT activity <60% of normal control, T-bili >3.0 mg/dL, and ALT >300 IU/L.	11	Corticosteroids, ≥60 mg prednisolone daily, was administered within 10 days after the diagnosis of severe disease using the above-mentioned criteria. The dosage of prednisolone was maintained at least for 4 days. When the patients showed a trend toward remission in PT, the dosage was reduced by 10 mg at least every 4 days to 30 mg. Then, the dosage was reduced by 2.5 or 5 mg every 2 wk or longer, depending on the decreasing trend of the ALT level.	11	42.5±12.9 vs 50.8±11.9	Single center, prospective cohort study	No	Japan
Fujiwara et al[18]	2000–2015	2	ALF was diagnosed based on the diagnostic criteria for ALF in Japan (2011), as follows: PT of 40% the standardized value, or an INR of ≥1.5 due to severe liver damage within 8 wk after the onset of disease symptoms, where the liver function before the current onset of liver damage was estimated to be normal based on blood laboratory data and imaging examinations.	14	High-dose corticosteroids therapy with 1000 mg of methylprednisolone or 60 mg of prednisolone, daily (as the initial dose) was administered. The dose was reduced according to the treatment response.	5	50.0±9.5 vs 32.0±18.0	Single center, retrospective cohort study	No	Japan
Chen et al[17]	2009–2012	12	Patients diagnosed as acute-on-chronic liver failure according to the Asian Pacific Association for the Study of the Liver 2009, positive for serum hepatitis B surface antigen, with the ALT level ≥20 ULN, receiving treatment within 2 wk after onset, and 16 to 65 years of age were eligible for inclusion.	31	Underwent an additional injection of dexamethasone for the first 3 days (10 mg/day/person) intravenously.	35	39.5±11.9 vs 36.9±11.3	Single center, retrospective cohort study	No	China

(*continued*)

Table 1

(continued).

Trial[17–24]	Enrolling period	Follow-up, wek	Inclusion criteria	Corticosteroid group, patient number	Corticosteroid therapy regimen	Regular therapeutic group, patient number	Age, years (Case group vs control group)	Study characteristics	Liver biopsy	Country
Reichen et al[21]	NC	52	Diagnosis of severe acute hepatic failure: alanine aminotransferase at least twice the ULN, replicating HBV infection documented for at least 6 mo and chronic active hepatitis on a biopsy no older than 3 mo at entry into the study.	18	Received 50 mg of prednisone for 2 wk, followed by 25 mg for another 2 wk. After a 2-wk, drug-free interval, recombinant interferon alpha 2b (Intron A) was injected subcutaneously 3 times weekly at a dose of 1.5 MU for 4 mo.	19	38 ± 13 vs 43 ± 15	Multicenter, prospective RCT	Yes	Switzerland
Kotoh et al[20]	2002–2006	5	Diagnosis of severe acute hepatic failure, fulfiling at least one of the following criteria: progressive and sustained PT (PT-INR >1.5 for >3 days), presence of ascites and hepatic encephalopathy.	17	After insertion of the catheter, 1000 mg methylprednisolone was infused for 2 h per day. The arterial steroid injections were continued for 3 days, and the catheter was removed just after injection on the third day.	17	45.1 ± 16.9 vs 44.8 ± 19.0	Single center, prospective cohort study	No	Japan
Zhang et al[23]	2006–2013	104	The eligible patients had been diagnosed with HBV-associated cirrhosis, and had a serum HBV DNA-level of >500 IU/mL. The patients had compensated liver cirrhosis and severe thrombocytopenia (defined as a platelet count of <30,000 cells/mm^3), accompanied by a tendency toward bleeding (including petechia, ecchymosis, hemoptysis, hematemesis, and hematochezia).	57	Prednisone was given at a dosage of 0.5mg/kg/day for 4 wk until a response was observed or until the side effects become intolerable. Patients who attained response continued the treatment for 4 wk thereafter. The dose was then tapered by 5 mg every 4 wk to a dosage of 10 mg/day, which was maintained for 4 to 6 months. The dose was then tapered over 6 to 8 wk until complete discontinuation.	46	43.2 ± 14.1 vs 40.3 ± 11.5	Multicenter, retrospective cohort study	Yes	China
Zhang et al[24]	2004–2008	4	HBV patients had not received any antiviral treatment with interferon or NA within 12 months; serum T-bili of ≥171 mmol/L; PTA of >40%; and serum ALT of ≥10 times compared with the ULN in 2 wk and >5 times compared with	56	Patients in the glucocorticoid group were immediately injected with dexamethasone (10 mg/day, i.v.) for 5 days on the basis of LMV and traditional supporting treatments after being enrolled.	114	37.1 ± 9.7 vs 39.7 ± 10.2	Single center, prospective RCT	No	China

(*continued*)

Table 1
(continued).

Trial[17–24]	Enrolling period	Follow-up, wek	Inclusion criteria	Corticosteroid group, patient number	Corticosteroid therapy regimen	Regular therapeutic group, patient number	Age, years (Case group vs control group)	Study characteristics	Liver biopsy	Country
			the ULN at the initiation of treatment							
Wu et al[22]	2005–2009	4	HBV patients serum T-bili level 262.5~436.3 mmol /L, serum albumin 32.4~34.3g/L, and thrombin activity 33.5%~38.7%	43	Patients in the glucocorticoid treatment group were given 10 mg/day glucocorticoid (dexamethasone) intravenous injection at the beginning of treatment, and dexamethasone was discontinued in 1 wk of treatment.	44	31.9 ± 7.7 vs 32.5 ± 8.2	Single center, prospective RCT	No	China

ALT = alanine aminotransferase, ALF = acute liver failure, INR = international normalized ratio, HBV = hepatitis B virus, NC = not clear, PT = prothrombin time, RCT = randomized controlled trial, T-bili = total bilirubin, ULN = upper limits of normal.

For the comparison of baseline data, a total of 538 patients were enrolled, and the males accounted for 72.9% in the corticosteroid treatment group and 84.9% in the regular treatment group. The I^2 test of heterogeneity was not significant (0%). A significantly greater number of males was noted than females in the regular treatment group (OR: 0.56; 95% CI: 0.36–0.88; $P = .01$) (Fig. 1). Moreover, a significant difference was observed in the age of patients between the 2 treatment groups. The age of patients in the regular treatment group was older than the corticosteroid treatment group (OR: −1.99; 95% CI: −3.83 to −0.14; $P = .04$) (Fig. 2). No significant heterogeneity was found ($I^2 = 18\%$). The sensitivity analysis showed consistent outcomes.

3.2. Efficacy of different treatment groups

The recovery of liver function was evaluated by comparing the decreasing effects on the ALT, T-bili, and PT levels of these 2 different treatment strategies. Our results showed no statistically significant differences in the ALT level before treatment (OR: −60.71; 95% CI: −159.24 to 37.83; $P = .23$) (Fig. 3). The I^2 test of heterogeneity was not significant (0%). The ALT levels were reduced in both groups after treatment, without significant differences in the reducing effects on ALT (OR: 4.51; 95% CI: −42.71 to 51.73; $P = .85$) (Fig. 3). The I^2 test of heterogeneity was significant (68%), and therefore the random-effects model was selected. Moreover, the T-bili levels between the 2 groups before treatment were not significantly different (OR: −0.97; 95% CI: −2.56 to 0.62; $P = .23$) (Fig. 4). The I^2 test of heterogeneity was 58%, and the random-effects model was selected. The T-bili level was significantly reduced in the corticosteroid treatment group compared with the regular treatment group (OR: −8.83; 95% CI: −14.99 to 2.67; $P = .005$) (Fig. 4). The I^2 test of heterogeneity was 91%, and the random-effects model was selected. Furthermore, PT was significantly long in both groups before treatment, with no significant differences (OR: 0.28; 95% CI: −0.79 to 1.34; $P = .61$) (Fig. 5). The I^2 test of heterogeneity was significant (37%). After treatment, PT was significantly shortened in the regular treatment group compared with the corticosteroid treatment group (OR: 31.71; 95% CI: 3.62–59.81; $P = .03$) (Fig. 5). The I^2 test of heterogeneity was significant (97%), and the random-effects model was selected.

The infection severity was evaluated by comparing the HBV DNA levels. Our results showed that the HBV DNA levels were high in both groups, without no significant differences (OR: 0.1; 95% CI: −0.24 to 0.44; $P = .56$) (Fig. 6). However, after treatment, the HBV DNA levels decreased significantly in both groups, but with no statistically significant differences (OR: −0.03; 95% CI: −019 to 0.13; $P = .71$) (Fig. 6).

3.3. Adverse event endpoints

The outcomes of both treatments were assessed by comparing the inpatient mortality, bleeding events, and ascites. Our results showed that inpatient mortality was significantly lower in the corticosteroid treatment group than the regular treatment group (OR: 0.23; 95% CI: 0.08–0.67; $P = .007$) (Fig. 7). Although PT was shorter in the corticosteroid treatment group than the conventional treatment group after treatment (OR: 31.71; 95% CI: −14.99 to 2.67; $P = .005$) (Fig. 8), there were no significant differences in bleeding events between these 2 groups (OR: 0.96;

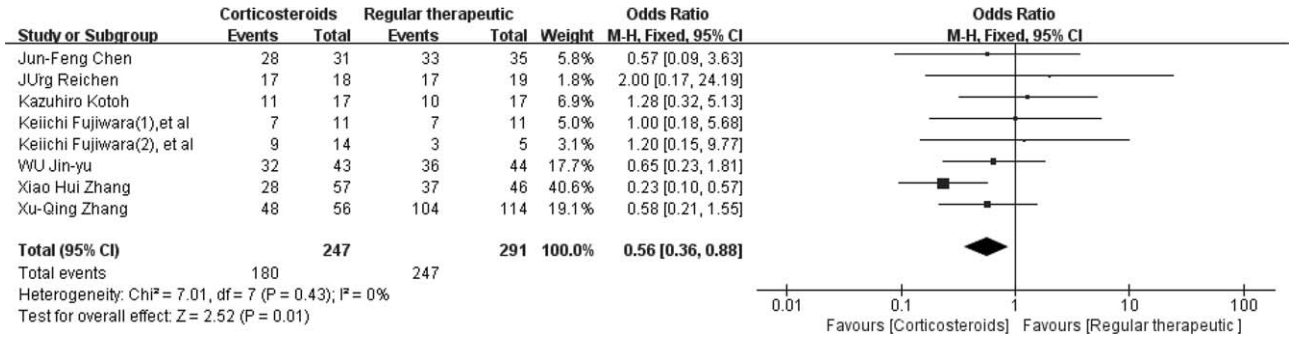

Figure 1. Sex difference in trials.

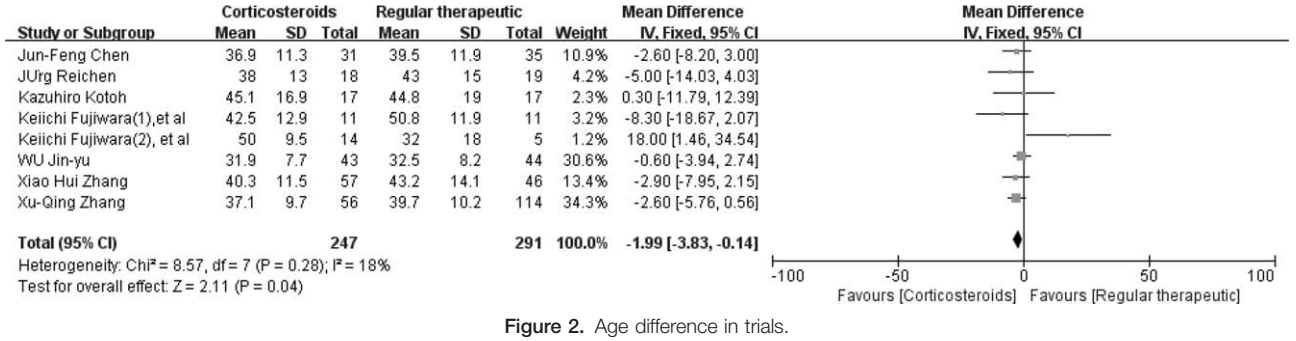

Figure 2. Age difference in trials.

95% CI: 0.48–1.92; $P = .001$). The cases of ascites events were significantly reduced in the corticosteroid treatment group (OR: 0.35; 95% CI: 0.18–0.67; $P = .90$) (Fig. 9). In addition, there was no significant difference in hospitalization duration (OR: −20.54; 95% CI: −46.35 to 5.27; $P = .12$) (Fig. 10).

3.4. Risk of bias in the included studies

The qualities of the studies included in this meta-analysis showed insignificant difference (Table 2). Five studies had unclear random sequence generation. Two studies had a high risk, whereas the remaining studies had a low risk. Six studies had a

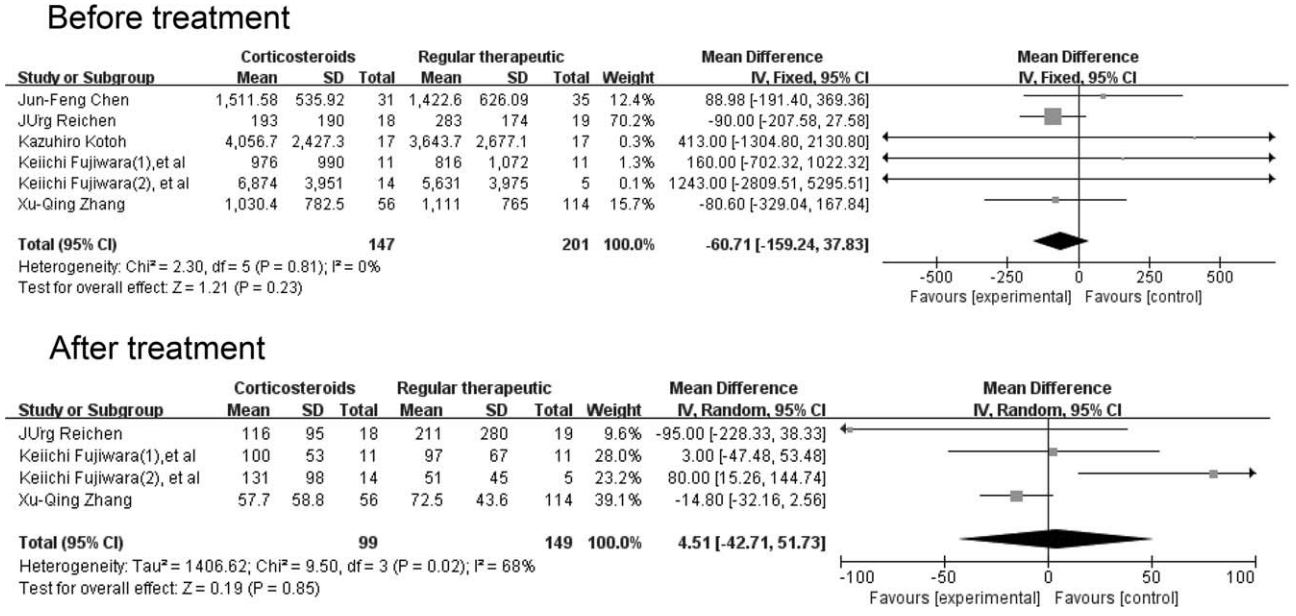

Figure 3. ALT level difference in trials before and after treatment. ALT = alanine transaminase.

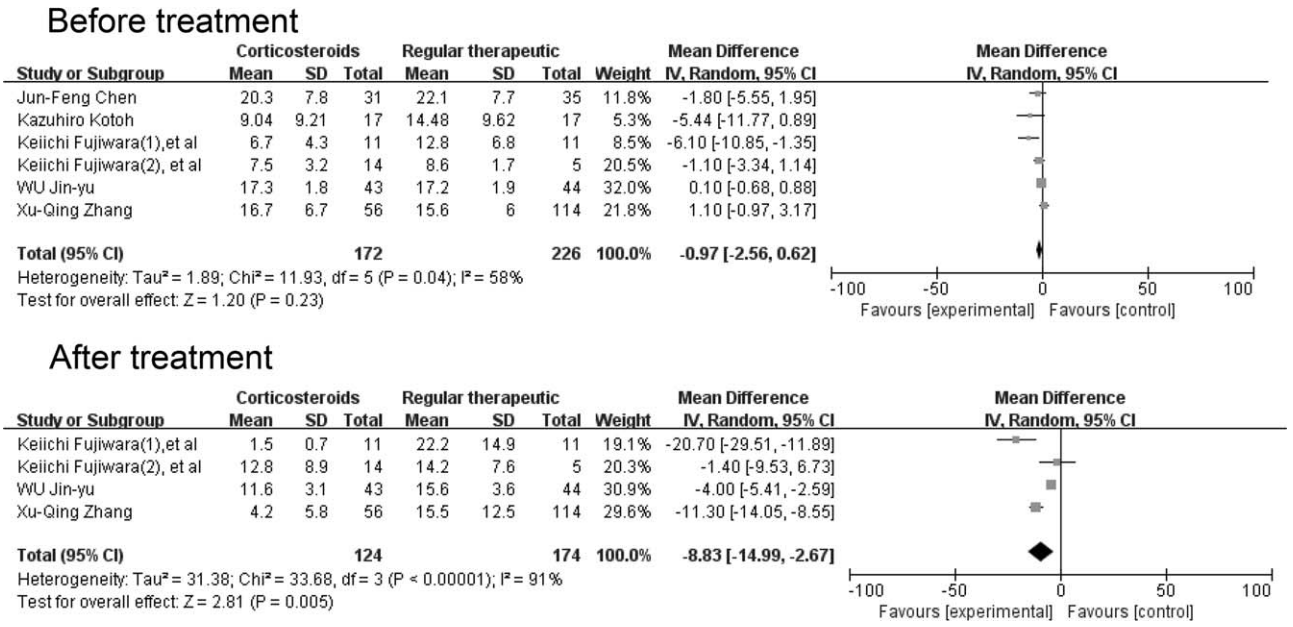

Figure 4. T-bili difference in trials before and after treatment. T-bili = total bilirubin.

low risk in the allocation concealment method, whereas the remaining studies had a high risk. The blinding design for the participants and personnel in the 6 studies was unclear, and 2 studies had high risks. Since different studies had different outcomes and comparison results, often without full statistical details, not all the data were suitable for the meta-analysis. Risk of bias is shown in Supplementary Figs. 2–3, http://links.lww.com/MD/E342, http://links.lww.com/MD/E343. The funnel plots of the study results for every with 95% confidence limits showed no bias. No obvious publication bias was found in our meta-analysis.

3.5. Sensitivity and heterogeneity analysis

Sensitivity analyses confirmed no inconsistency of our main findings. Meta-regression analysis showed that patient type had no effect on any endpoints for the corticosteroid treatment group versus the regular treatment group.

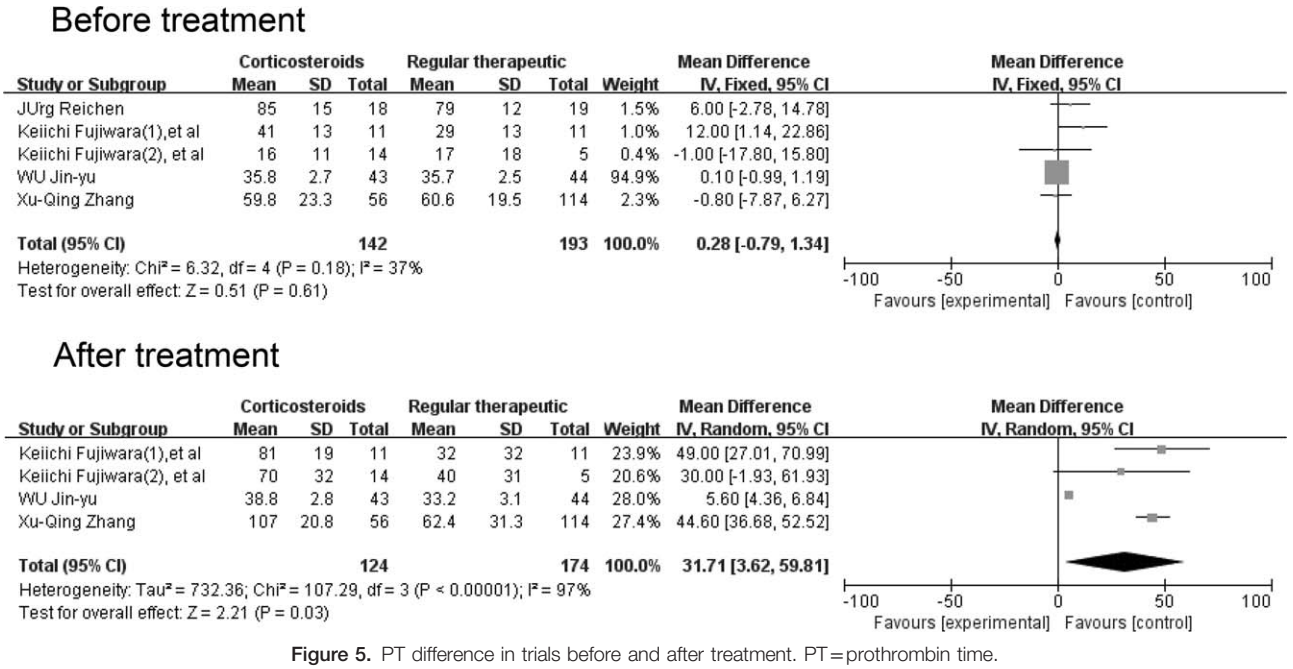

Figure 5. PT difference in trials before and after treatment. PT = prothrombin time.

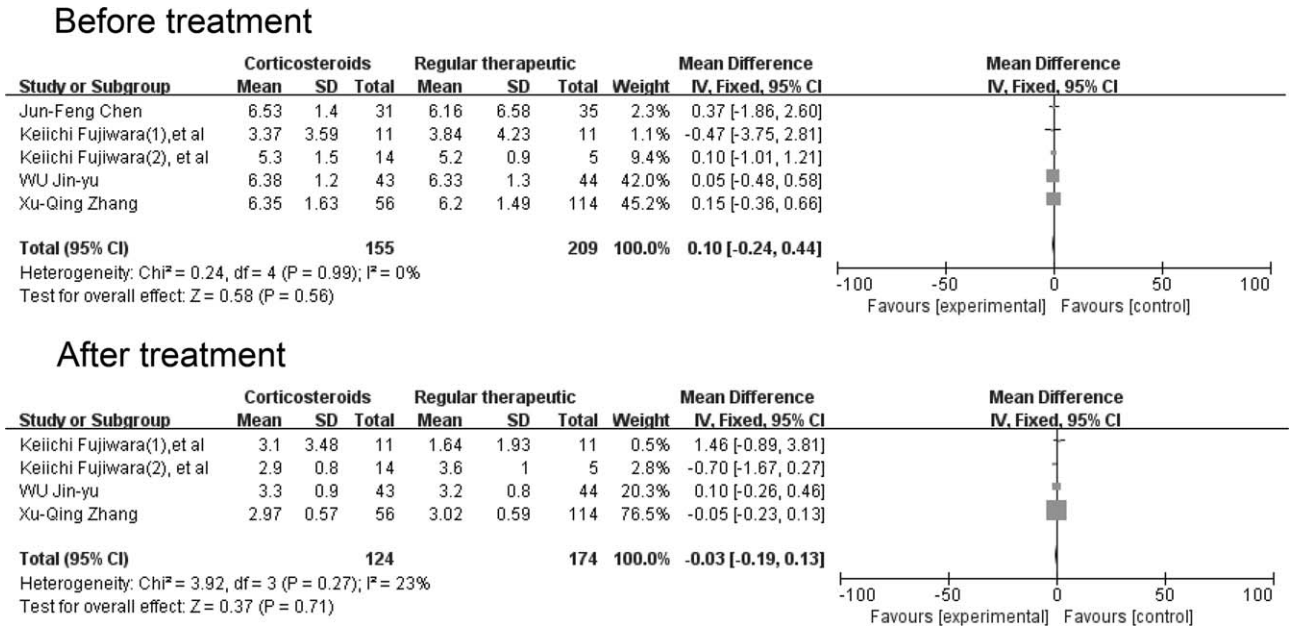

Figure 6. HBV DNA difference in trials before and after treatment. HBV = hepatitis B virus.

4. Discussion

Comparing the baseline data for the 2 patient groups, our results showed that the majority of the patients in these 2 groups were male, and there were more males in the glucocorticoid treatment group than in the regular treatment group. In addition, patient average age was significantly higher in the regular treatment group. Risk factors (ie, the ALT, T-bili, PT, and HBV DNA levels) were compared and analyzed, and were shown to have clear impact on liver function and disease prognosis in patients with HBV-related liver failure. There was no significant difference in the level of these risk factors among the patients before treatment. However, after treatment, T-bili level was significantly decreased in the glucocorticoid treatment group, and PT was significantly shortened in the regular treatment group. Most importantly, our results showed that glucocorticoid treatment significantly reduced in-hospital mortality and ascites events.

HBV-related ACLF refers to an acute hepatic insult in patients with chronic liver disease or cirrhosis (diagnosed or undiagnosed), which might to lead to jaundice and coagulopathy complicated by clinical ascites and/or encephalopathy due to HBV activation.[25] Since the pathogenesis of ACLF involves systemic inflammation and susceptibility to infection, the risk factors for ACLF mainly fall into 2 categories, that is, the intrahepatic factors (such as HBV reactivation and alcohol consumption) and the extrahepatic factors (such as bacterial infection).[26–28] Because sex is not a risk factor for ACLF, it had little influence on the study results. The meta-analysis of the diagnostic criteria for ACLF showed that increased age was associated with the poor outcomes.[29] The age of patients was significantly higher in the regular treatment group, which was a protective factor for ACLF patients. Therefore, the age difference did not affect the study results.

Glucocorticoid therapy for viral hepatitis began in 1951.[30] However, the results have been controversial,[31–33] and the controversial results might be attributed to the disease cause, drug dosage, and time from initiation to cessation.[29,34] To exclude the influence of different etiologies on outcomes, only the meta-analysis for HBV-related ACLF population was performed. The efficacies of the 2 strategies in treating ACLF were analyzed and compared, and our results showed that T-bili was

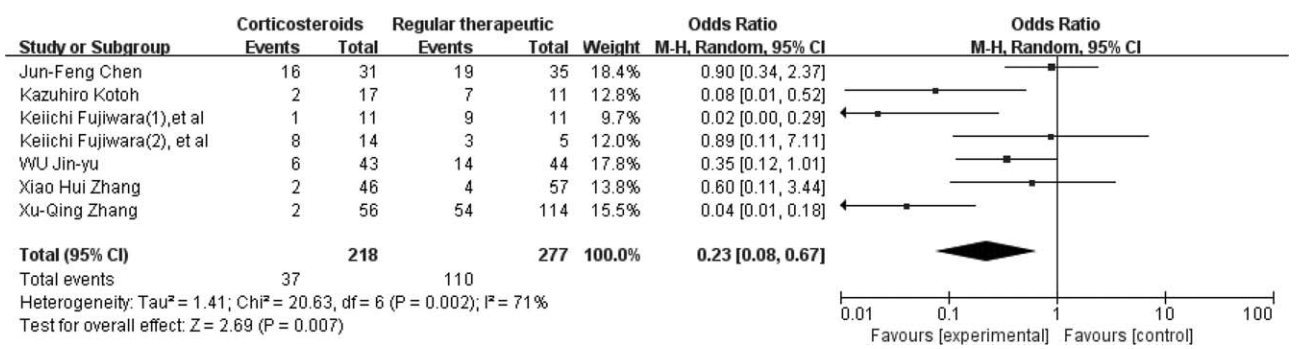

Figure 7. Inpatient mortality difference in trials.

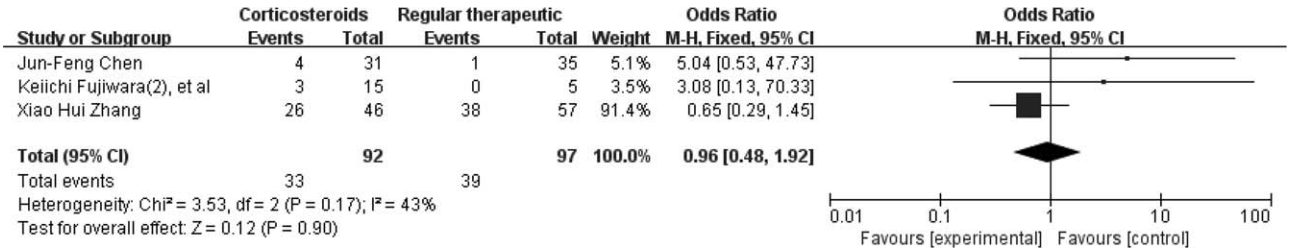

Figure 8. Bleeding event difference in trials.

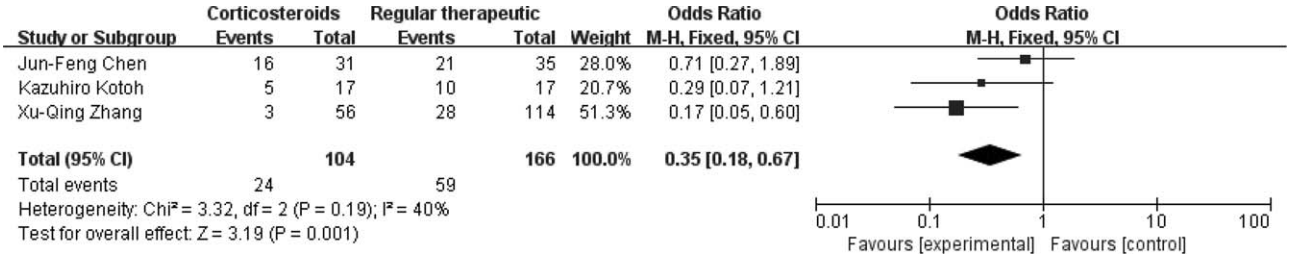

Figure 9. Ascites event difference in trials.

significantly reduced in the glucocorticoid treatment group, whereas the recovery of PT was better in the regular treatment group. Production of bilirubin from heme catabolism would exhibit neurotoxicity and cytotoxicity in various cell types. Studies have shown that bilirubin also has antioxidant effects.[16,35] In patients with ACLF who develop to liver failure, the liver dysfunction would lead to the production of large amounts of bilirubin in the blood. The cytotoxicity of bilirubin aggregation can further aggravate the liver failure and lead to hepatic encephalopathy. Therefore, despite the antioxidant properties of bilirubin, its cytotoxicity should be considered first since ACLF pathogenesis progresses rapidly. In our meta-analysis concerning the T-bili levels in patients with HBV-associated ACLF, our results showed that glucocorticoid reduced T-bili, better than conventional therapy. A previous meta-analysis of 5 studies has shown that T-bili levels in patients with virus-associated ACLF are positively correlated with admission mortality.[29] In this study, our results showed no significant difference in ALT and HBV-DNA levels between the 2 groups before and after treatment, and patient mortality was significantly decreased in the glucocorticoid treatment group during hospitalization. These results suggest that there is no significant difference in the hepatocyte rupture induced by HBV infection between the 2 groups. Therefore, the increased mortality in patients with acute ACLF episodes may be due to the increased T-bili level. Since glucocorticoid therapy can significantly reduce T-bili compared with conventional therapy in a short period, it is of great significance to grasp the timing and treatment measures.

As one evaluation items for blood coagulation, the PT activity degree mainly reflects the content of coagulation factors II, V, VII, and X, or the presence of circulating anticoagulant substances, which are mainly synthesized by the liver.[36] When hepatocytes are severely damaged and/or lost, the reduced ability of the liver to synthesize these substances would lead to decreased coagulation factor levels and prolonged PT. Therefore, PT can reflect the liver synthesis function. Thrombomodulin, a transmembrane protein located on vascular endothelial cells, can activate protein C (with anticoagulant effects) and regulate the synthesis of thrombin (with procoagulant effects),[37–39] that is, thrombomodulin has both anticoagulant and procoagulant effects. However, laboratory tests for PT only measure the amount of thrombin generated in plasma to act as the procoagulant driver, but not protein C, which is not fully activated in the absence of thrombomodulin. This phenomenon would also explain why

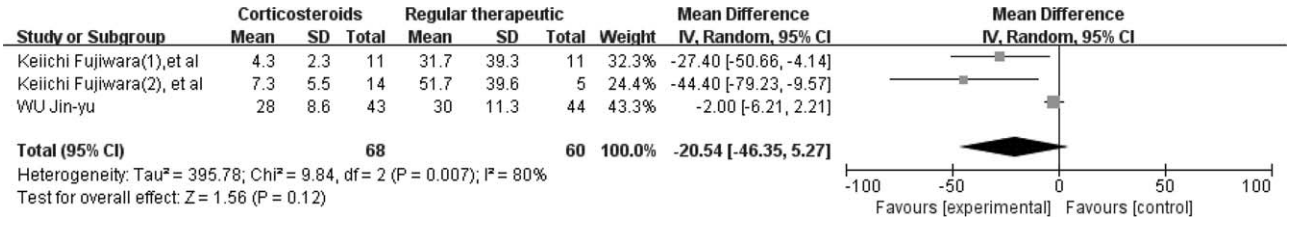

Figure 10. In hospital duration difference in trials.

Table 2

Risk of bias of included randomized controlled trials.

Trial[17–24]	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcomes assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fujiwara et al[19]	2004	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Fujiwara et al[18]	2018	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Chen et al[17]	2013	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Reichen et al[21]	1992	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Kotoh et al[20]	2006	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Zhang et al[23]	2014	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Zhang et al[24]	2011	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Wu et al[22]	2011	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk

there was significant difference in PT between the 2 groups after treatment, but no significant difference in bleeding events. Studies have shown that increased glucocorticoid levels in the blood can inhibit the hypothalamic-pituitary-adrenal axis, which would result in decreased levels of tumor necrosis factor-α, interleukin (IL)-2, IL-6, and other pro-inflammatory cytokines.[40] Thrombin is a key protein in the coagulation cascade pathway. When pro-inflammatory cytokine levels in the blood are downregulated, thrombin will be activated to induce the compensatory secretion of pro-inflammatory cytokines by human adipocytes, monocytes/macrophages, and vascular endothelial cells.[41] The correlation between the coagulation and immune systems could provide a theoretical basis for the explanation of PT prolongation in the glucocorticoid treatment group.

The pathogenesis of ACLF is very complex, mainly caused by the immune reaction, hepatic microcirculation disorder, and endotoxemia. Glucocorticoid, through the glucocorticoid receptor, can inhibit the immune response and reduce hepatocyte damage. Cytotoxic T lymphocytes are the main effector cells in patients with liver failure, and activated cytotoxic T lymphocytes can directly kill the target cells, causing hepatocyte necrosis or apoptosis.[42] Kim et al[43] have found that the glucocorticoid receptor upregulates fibronectin type III domain 5 (FNDC5) expression via peroxisome proliferator-activated receptor gamma coactivator 1-alpha, preventing liver lipid deposition and autophagic dysfunction in mice, which could protect liver function.

Glucocorticoid has been widely used in the clinic in recent years, with a positive effect on septic shock.[44] However, the efficacy of glucocorticoid in the treatment of HBV-associated ACLF is controversial. A randomized controlled clinical study has shown that glucocorticoid therapy does not improve the prognosis or reduce mortality in HBV-related ACLF, and it could only recover blood hemodynamics. However, the patients included in this study were in the middle or late stages of liver failure. Many studies have shown that glucocorticoids are used intermittently or continuously for a long time in HBV-related ACLF patients, achieving a satisfactory prognosis.[19,45] Risks of infection, gastrointestinal bleeding, and HBV amplification were not increased. In these studies, patients with early liver failure were selected.[19,45] The efficacy and safety of glucocorticoid for HBV-related ACLF patients are certain, especially for the early stage of ACLF.

This is the first meta-analysis of glucocorticoid therapy for HBV-related ACLF patients. Our study included 3 RCTs and 5 cohort studies, 3 of which were retrospective cohort studies, with relatively small sample sizes. Although the number of RCT studies included was small and the impact of the findings on guidelines and clinical interventions might be insufficient, our findings provide useful evidence to guide the design of subsequent prospective RCTs in the future. In addition, we searched the literature and found that HBV associated hepatitis was much more prevalent in the Western Pacific (6.2% or 115 million individuals suffering from chronic HBV infection) and African (6.1% or 60 million individuals) regions, due to the special geographical location and poor public health development.[46] Our findings apply only to East Asian populations.

There are also several limitations to this study. First, 3 of the included articles were single-center retrospective studies, which would lead to an insufficient level of evidence for the analysis. Secondly, the glucocorticoid treatment group included in the study did not have a unified program, and there were differences in the type of treatment program and course, which may affect the results. Third, ACLF progressed rapidly and had a high mortality rate. Many patients had already suffered from advanced liver failure before the treatment. Therefore, the number of samples included in those included studies was relatively small, which could increase the probability of type II errors in the statistical analysis.

In conclusion, this meta-analysis included a total of 538 patients, enrolled in 3 RCT and 5 cohort studies. The glucocorticoid and conventional treatments for the early stage of HBV-related ACLF patients were analyzed and compared. Our results showed that glucocorticoid treatment was more effective in reducing the T-bili level, and decreasing in-hospital mortality and ascites. Patient mortality was consistent with the T-bili level, suggesting that bilirubin may play a very important role in the progression to advanced liver failure in early-stage HBV-related ACLF patients.

Author contributions

Conceptualization: Xiaobo Lu.
Data curation: Li Tang, Jianzhong Yang.
Formal analysis: Yang Li, Rongjiong Zheng.
Funding acquisition: Xiaobo Lu.
Methodology: Jianzhong Yang.
Resources: Li Tang.
Supervision: Xiaobo Lu.
Visualization: Ranran Gao.

Writing – original draft: Yang Li, Yang Cao, Rongjiong Zheng. **Writing – review & editing:** Ranran Gao.

References

[1] Sarin SK, Kedarisetty CK, Abbas Z, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014;8:453–71.

[2] Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care 2011;17:165–9.

[3] Sarin SK, Choudhury A. Management of acute-on-chronic liver failure: an algorithmic approach. Hepatol Int 2018;12:402–16.

[4] Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. Nat Rev Gastroenterol Hepatol 2016;13: 131–49.

[5] Choudhury A, Jindal A, Maiwall R, et al. Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. Hepatol Int 2017;11:461–71.

[6] Czaja AJ, Davis GL, Ludwig J, et al. Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. Hepatology 1984;4:622–7.

[7] Fujiwara K, Yasui S, Okitsu K, et al. The requirement for a sufficient period of corticosteroid treatment in combination with nucleoside analogue for severe acute exacerbation of chronic hepatitis B. J Gastroenterol 2010;45:1255–62.

[8] He B, Zhang Y, Lu MH, et al. Glucocorticoids can increase the survival rate of patients with severe viral hepatitis B: a meta-analysis. Eur J Gastroenterol Hepatol 2013;25:926–34.

[9] McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA 2018;319:388–96.

[10] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[11] Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.

[12] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[13] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.

[14] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[15] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[16] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[17] Chen JF, Wang KW, Zhang SQ, et al. Dexamethasone in outcome of patients with hepatitis B virus-related acute-on-chronic liver failure. J Gastroenterol Hepatol 2014;29:800–6.

[18] Fujiwara K, Yasui S, Haga Y, et al. Early combination therapy with corticosteroid and nucleoside analogue induces rapid resolution of inflammation in acute liver failure due to transient hepatitis B virus infection. Intern Med 2018;57:1543–52.

[19] Fujiwara K, Yokosuka O, Kojima H, et al. Importance of adequate immunosuppressive therapy for the recovery of patients with "life-threatening" severe exacerbation of chronic hepatitis B. World J Gastroenterol 2005;11:1109–14.

[20] Kotoh K, Enjoji M, Nakamuta M, et al. Arterial steroid injection therapy can inhibit the progression of severe acute hepatic failure toward fulminant liver failure. World J Gastroenterol 2006;12:6678–82.

[21] Reichen J, Bianchi L, Frei PC, et al. Efficacy of steroid withdrawal and low-dose interferon treatment in chronic active hepatitis B. Results of a randomized multicenter trial. Swiss Association for the Study of the Liver. J Hepatol 1994;20:168–74.

[22] Wu JY, Li M, Zhang H. [Effect of glucocorticoid treatment on the clinical outcome of patients with early-stage liver failure]. Nan Fang Yi Ke Da Xue Xue Bao 2011;31:554–6.

[23] Zhang XH, Feng R, Xu LP, et al. Immunosuppressive treatment combined with nucleoside analog is superior to nucleoside analog only in the treatment of severe thrombocytopenia in patients with cirrhosis associated with hepatitis B in China: a multicenter, observational study. Platelets 2015;26:672–9.

[24] Zhang XQ, Jiang L, You JP, et al. Efficacy of short-term dexamethasone therapy in acute-on-chronic pre-liver failure. Hepatol Res 2011;41:46–53.

[25] Bajaj JS, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure: getting ready for prime time? Hepatology 2018;68:1621–32.

[26] Bernal W, Jalan R, Quaglia A, et al. Acute-on-chronic liver failure. Lancet 2015;386:1576–87.

[27] Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–37.

[28] Shi Y, Yang Y, Hu Y, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. Hepatology 2015;62:232–42.

[29] Wlodzimirow KA, Eslami S, Abu-Hanna A, et al. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. Liver Int 2013;33:40–52.

[30] Ducci H, Motlis J. [Fulminant hepatitis; recovery]. Rev Med Chil 1951;79:590–4.

[31] Gregory PB, Knauer CM, Kempson RL, et al. Steroid therapy in severe viral hepatitis. A double-blind, randomized trial of methyl-prednisolone versus placebo. N Engl J Med 1976;294:681–7.

[32] Ware AJ, Cuthbert JA, Shorey J, et al. A prospective trial of steroid therapy in severe viral hepatitis. The prognostic significance of bridging necrosis. Gastroenterology 1981;80:219–24.

[33] Ware AJ, Jones RE, Shorey JW, et al. A controlled trial of steroid therapy in massive hepatic necrosis. Am J Gastroenterol 1974;62:130–3.

[34] Bajaj JS. Defining acute-on-chronic liver failure: will East and West ever meet? Gastroenterology 2013;144:1337–9.

[35] Idelman G, Smith DLH, Zucker SD. Bilirubin inhibits the up-regulation of inducible nitric oxide synthase by scavenging reactive oxygen species generated by the toll-like receptor 4-dependent activation of NADPH oxidase. Redox Biol 2015;5:398–408.

[36] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365:147–56.

[37] D'Alessio S, Genua M, Vetrano S. The protein C pathway in intestinal barrier function: challenging the hemostasis paradigm. Ann N Y Acad Sci 2012;1258:78–85.

[38] Tripodi A, Primignani M, Chantarangkul V, et al. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology 2006;44:440–5.

[39] Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41:553–8.

[40] Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol 2017;17:233–47.

[41] Ma L, Dorling A. The roles of thrombin and protease-activated receptors in inflammation. Semin Immunopathol 2012;34:63–72.

[42] Yamamiya D, Mizukoshi E, Kaji K, et al. Immune responses of human T lymphocytes to novel hepatitis B virus-derived peptides. PLoS One 2018;13:e0198264.

[43] Kim HK, Jeong YJ, Song IS, et al. Glucocorticoid receptor positively regulates transcription of FNDC5 in the liver. Sci Rep 2017;7:43296.

[44] Arabi YM, Aljumah A, Dabbagh O, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ 2010;182:1971–7.

[45] Zhao B, Xie GJ, Li RF, et al. Dexamethasone protects normal human liver cells from apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand by upregulating the expression of P-glycoproteins. Mol Med Rep 2015;12:8093–100.

[46] Yuen M, Chen D, Dusheiko Geoffrey M. Hepatitis B virus infection. Nat Rev Dis Primers 2018;4:18035.