

# Effectiveness of granulocyte colony-stimulating factor for patients with acute-on-chronic liver failure: a meta-analysis

Wei Huang, Yuanji Ma, Lingyao Du, Shuang Kang, Chang-Hai Liu, Lang Bai, Xuezhong Lei, Hong Tang

From the Center of Infectious Diseases, West China Hospital of Sichuan University, Chengdu, China

**Correspondence:** Dr. Hong Tang · Center of Infectious Diseases, West China Hospital, Sichuan University, No.37 Guoxue Alley, Chengdu, Sichuan Province, 610041, China · htang6198@hotmail.com · ORCID: <https://orcid.org/0000-0002-9790-6225>

**Citation:** Huang W, Ma Y, Du L, Kang S, Liu CH, Bai L, et al. Effectiveness of granulocyte colony-stimulating factor for patients with acute-on-chronic liver failure: a meta-analysis. *Ann Saudi Med* 2021; 41(6): 383-391. DOI: 10.5144/0256-4947.2021.383

**Received:** March 8, 2021

**Accepted:** July 9, 2021

**Published:** December 2, 2021

**Copyright:** Copyright © 2021, *Annals of Saudi Medicine*, Saudi Arabia. This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND). The details of which can be accessed at <http://creativecommons.org/licenses/by-nc-nd/4.0/>

**Funding:** 1.3.5 Project for disciplines of excellence, West China Hospital, Sichuan University x ZYGD20009 Prevention and treatment of AIDS, viral hepatitis and other infectious diseases x 2018ZX10715003

**BACKGROUND:** The safety and efficacy of granulocyte colony-stimulating factor (G-CSF) for the treatment of acute-on-chronic liver failure (ACLF) remain uncertain. Therefore, we conducted a meta-analysis to draw a firmer conclusion.

**METHODS:** We searched the Cochrane library, PubMed, Embase, and China Biology Medicine disc to identify relevant RCTs performed before January 2020. Risk ratios (RRs) and their 95% confidence intervals (95% CIs) were calculated using a random effects model.

**MAIN OUTCOME MEASURES:** RRs (95% CI) for 1-, 2-, and 3-month survival rates.

**SAMPLE SIZE:** Six RCTs, including three open-label studies.

**RESULTS:** The six studies included 246 subjects (121 in a G-CSF group and 125 in a control group). G-CSF administration significantly improved the 1-, 2-, and 3-month survival rates in patients with ACLF. The pooled RRs (95% CI, P) were 0.43 (0.27–0.69,  $P=.0004$ ), 0.44 (0.32–0.62,  $P<.00001$ ), and 0.39 (0.22–0.68,  $P=.0009$ ), respectively.

**CONCLUSION:** G-CSF may be beneficial and effective in the treatment of ACLF, but further studies are needed to verify this conclusion.

**LIMITATIONS:** The sample size was small, and studies were restricted to countries in Asia.

**PROSPERO REGISTRATION NUMBER:** CRD42021225681

**CONFLICT OF INTEREST:** None.

End-stage hepatic injury constitutes liver failure due to various causes; acute-on-chronic liver failure (ACLF) was added as a new classification of liver failure in 1995.<sup>1</sup> ACLF is an acute liver injury with a high 28-day mortality manifesting as coagulopathy and jaundice, complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis.<sup>2</sup> Non-infectious etiologies, such as hepatotoxic drugs, variceal bleeding, and alcoholic hepatitis, are the main causes of ACLF in the West. Conversely, infectious etiologies, including hepatitis B (HBV), hepatitis C, and superinfection with hepatitis E, are the main causes of ACLF in the East, but the occurrence of alcoholic hepatitis has also increased in Asian countries in recent years.<sup>2,3</sup> Regardless of the precipitating factor, patients with ACLF have an extremely poor prognosis; 28-day mortality ranges from 29.7% to 40%.<sup>4</sup> According to the consensus recommendations of the Asian Pacific Association,<sup>2</sup> there are three main treatments for ACLF: medication, an artificial liver,<sup>5</sup> and orthotopic liver transplantation (OLT). Currently, OLT is the last hope for patients, whose life cannot be prolonged by support therapies.<sup>2</sup> Worldwide clinical trials have shown that liver transplantation offered survival benefits for some patients with ACLF.<sup>6</sup> However, finding a suitable liver source for patients with ACLF before the availability of appropriate organ donors is difficult, so patients often have to go through long-term therapies with little effect. In cases like these, an artificial liver is a realistic and optional plan; however, the effects of the medicines and the artificial liver treatment need further study. Although there is a standardized process for artificial liver treatment, optimizing medicinal options has become the main research direction. Currently, efforts are directed towards facilitating liver regeneration and reducing cell apoptosis, using hepatocyte growth factor,<sup>7</sup> interleukin 6,<sup>8</sup> and granulocyte colony-stimulating factor (G-CSF). Research on G-CSF for the treatment of ACLF has been conducted at preclinical levels and in small-scale clinical trials, and research outcomes are optimistic. Therefore, G-CSF treatment for ACLF may be effective in extending survival for patients waiting for OLT.

Effective regeneration of hepatocytes plays a pivotal role in the successful treatment of liver failure. Animal experiments have demonstrated that G-CSF can promote liver repair and induce endogenous hepatic oval cell migration and proliferation.<sup>9</sup> Clinical results also show that G-CSF plays a certain role in improving the survival rate and prognosis of patients with liver failure.<sup>10-15</sup> In addition, G-CSF has been reported to pre-

vent complications, such as sepsis and multiorgan failure, which may be explained by improved neutrophil function and immunomodulation.<sup>13,15</sup>

Based on the reported clinical studies, G-CSF can improve prognosis and prolong survival rates in patients with ACLF; however, varying clinical conditions, a lack of representative samples, and small sample sizes in those studies preclude firm conclusions. Our goal was to analyze a larger sample by performing a meta-analysis limited to randomized controlled trials (RCTs), hoping to improve prognosis and optimize clinical management for ACLF.

## METHODS

### Search strategy

We gathered relevant studies by searching the databases of the Cochrane Library, PubMed, Embase, and the China Biology Medicine disc for studies published before January 2020, using the keywords: ("Granulocyte colony stimulating factor" or "Granulocyte Colony-Stimulating Factor" or "G-CSF" or "GCSF") and ("Liver failure" or "Hepatic failure" or "Severe hepatitis" or "Fulminant hepatitis" or "ACLF" or "Acute-on-chronic liver failure"). There were no restrictions on article type, publication date, or additional filters. The references of the retrieved articles were also searched. Our study was registered in PROSPERO (Registration number: CRD42021225681).

### Study selection

Two researchers independently reviewed the titles and abstracts of all retrieved literature to prepare a preliminary screening list. Two other reviewers then examined the full text and screened the list again. If any dispute or argument occurred, it was discussed or handed over to a senior author for evaluation, until a consensus was reached. Finally, two reviewers extracted the variables for analysis, including the first author's name, country and year of study, causes, range (mean) age, sex, enrollment period, sample size, diagnostic criteria, drug route/dose, and adverse reactions. The primary outcome measures, such as 1-, 2-, and 3-month survival rates for severe alcoholic hepatitis and/or HBV-ACLF, were included.

### Inclusion and exclusion criteria

Studies were considered suitable for this meta-analysis if they met the following inclusion criteria: (i) clear ACLF diagnostic criteria on patients; (ii) the experimental group consisted of patients treated with G-CSF in combination with comprehensive medical treatment,

and the control group consisted of patients receiving only comprehensive medical treatment; (iii) the primary outcome was 1-, 2-, and 3-month survival rates of patients with severe alcoholic hepatitis and/or HBV-ACLF; (iv) the design was a randomized and controlled; (v) all cases had clear inclusion and exclusion criteria. The exclusion criteria were as follows: (i) non-randomized controlled study; (ii) non-therapeutic use of G-CSF; (iii) no clear inclusion and exclusion criteria; (iv) not reported in English; (v) articles were reviews, adverse reaction reports, and non-clinical trial studies on pharmacology.

### Statistical analysis

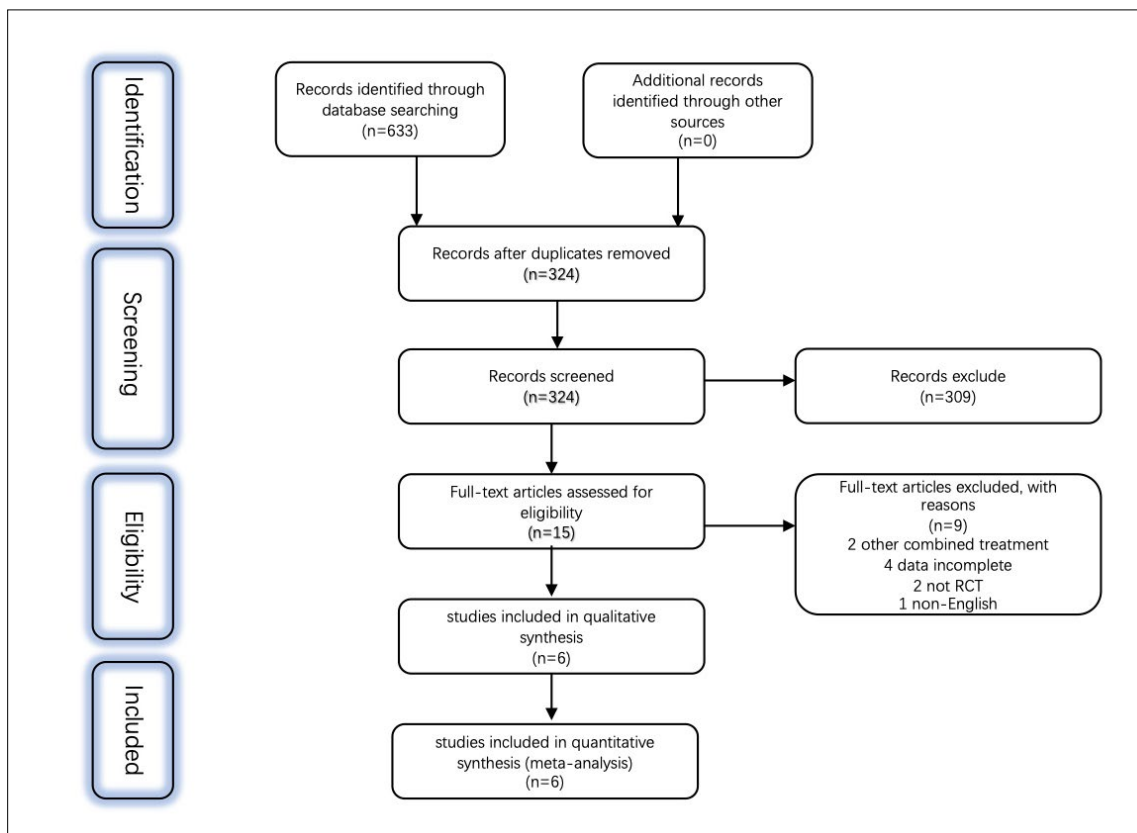
Meta-analysis and risk of bias was performed using Cochrane Review Manager Software (RevMan5.4). The therapeutic effect of G-CSF on ACLF was assessed by estimating the pooled risk ratios (RRs) and their 95% confidence intervals (CIs). If there was no heterogeneity, a Mantel-Haenszel fixed-effects model was used to calculate the pooled RRs, rather than a random-effects model. Heterogeneity of the included studies was checked using Cochran's test, and heterogeneity was considered significant if  $I_2 > 50\%$ . Subgroup analysis

was classified according to the different causes leading to ACLF. If the point estimate of the omitted analysis fell outside the 95% CI of the meta-analysis, potential publication bias was also examined qualitatively on a funnel plot.

## RESULTS

### Selection of studies and assessment of bias

The initial literature search conducted on 1 January 2020 retrieved 633 records (EMbase: 485; Pubmed: 93; Cochrane: 55) (**Figure 1**). After screening titles and abstracts and eliminating duplicate records, 324 records remained. We excluded 309 records that did not meet the eligibility criteria, which left 15 records. Nine full-text articles were excluded due to substandard assessment of treatment eligibility (two with combined treatment as confounding factors; four with missing data; two non-randomized controlled trials; one non-English report). Finally, the six studies selected for analysis included 246 patients from India,<sup>10-13</sup> China,<sup>14</sup> and Bangladesh (**Table 1**).<sup>15</sup> We found that the risk of bias was low or non-existent for most domains but unclear for detection bias



**Figure 1.** PRISMA flow diagram of the study.

**Table 1.** Baseline characteristics of the included studies.

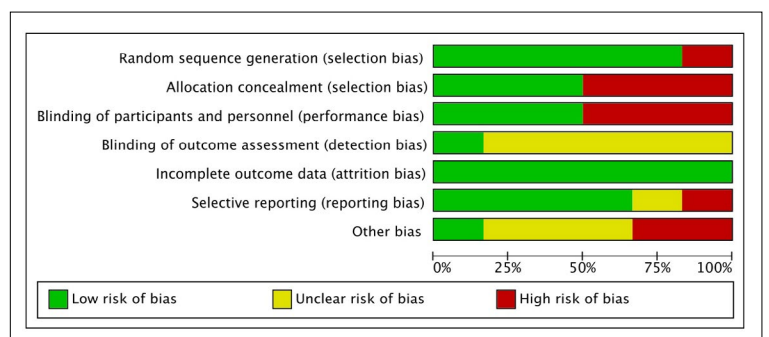
Author year	Country	Causes	Age range	Male	Period of enrollment	Sample size	Diagnostic criteria
Singh 2018 <sup>10</sup>	India	Severe alcoholic hepatitis	18~75	38	2014-2017	38	Abnormal liver function tests with a serum TBIL >5 mg/100 mL (86 µmol/L), an AST/ALT ratio > 2, an AST <301 U/L, a history of heavy alcohol use
Shasthry 2019 <sup>11</sup>	India	Severe alcoholic hepatitis	40.2±10.3	27	2013-2016	28	History of chronic alcohol abuse >5 years, jaundice, Maddrey's score >32, liver histology
Singh 2014 <sup>12</sup>	India	Severe alcoholic hepatitis	18~75	46	2010-2012	46	Abnormal liver function tests with a serum TBIL >5 mg/100 mL (86 µmol/L), an AST/ALT ratio >2, an AST <300 U/L, a history of heavy alcohol use
Grag 2012 <sup>13</sup>	India	Mixed	12~75	41	2008-2010	47	High SAAG, grade ≥2 esophageal varices, HVPG ≥10 mm Hg, stage ≥2 fibrosis on histologic analysis, or portal vein ≥13 mm Hg on ultrasonography
Duan 2013 <sup>14</sup>	China	Hepatitis B	18~65	44	2009-2011	55	Serum TBIL ≥5 mg/dL, INR ≥1.5 or PTA <40%, ascites and/or encephalopathy within 4 weeks, HBV-DNA ≥1 × 10 <sup>4</sup> copies/mL, HBs-Ag (+), ALT >5* (upper limit of normal value)
Saha 2017 <sup>15</sup>	Bangladesh	Mixed	>18	28	--	32	History of illness, clinical presentation, TBIL level >5.0 mg/dL, presence of coagulopathy (INR >1.5), ascites and encephalopathy

Author year	Drug route/dose	Adverse reaction	1-month survival rates (%)		2-month survival rates (%)		3-month survival rates (%)	
			Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Singh 2018 <sup>10</sup>	5 ug/kg subcutaneously every 12h for 5 consecutive days	4 bone pains, 1 headache, 1 rash and increasing spleen size	16/18(88.89)	11/20 (55.00)	16/18 (88.89)	8/20 (40.00)	16/18 (88.89)	6/20 (30.00)
Shasthry 2019 <sup>11</sup>	5 ug/kg daily to a maximum of 300 ug per day for 5 doses followed by every 3 day until 4 weeks (a total of up to 12 doses)	1 severe bone pain	11/14 (78.57)	10/14 (71.43)	10/14 (71.43)	5/14 (35.71)	9/14 (64.29)	4/14 (28.57)
Singh 2014 <sup>12</sup>	5 ug/kg subcutaneously every 12h for 5 consecutive days	3 bone pains, 2 headache	18/23 (78.26)	10/23 (43.48)	18/23 (78.26)	9/23 (39.13)	18/23 (78.26)	5/23 (21.74)
Grag 2012 <sup>13</sup>	5ug/kg subcutaneously, 12 doses over a period of 1 month (daily doses for the first 5 days and then every 3 day)	1 rash, 1 herpes zoster, 1 fever	18/23 (78.26)	11/24 (45.83)	16/23 (69.57)	7/24 (29.17)	--	--
Duan 2013 <sup>14</sup>	5 µg/kg per day for 6 consecutive days	8 fever, 5 headach,4 nausea	25/27 (92.59)	24/28 (85.71)	17/27 (62.96)	9/28 (32.43)	13/27 (48.15)	6/28 (21.43)
Saha 2017 <sup>15</sup>	5 ug/kg/day, for 6 consecutive days	--	14/16 (87.50)	13/16 (81.25)	14/16 (87.50)	13/16 (81.25)	14/16 (87.50)	8/16 (50.00)

because of inadequate reporting of blinding except in one study (Figure 2). Three studies were open label, which affected allocation concealment and blinding of participants and personnel.<sup>10,12,15</sup> Two studies were at high risk of other bias, because they did not report the G-CSF manufacturer.<sup>13,15</sup> None of the individual studies affected the pooled outcome excessively.

**Survival rates**

In the six eligible studies, the intervention methods were roughly commensurate, but the heterogeneity test across the six articles was statistically significant ( $P<.05$ ), so we used a random effects model to assess survival rates. The pooled RR (95% CI,  $P$ ) values of the 1-, 2-, and 3-month survival rates were 0.43 (0.27–0.69,  $P=.0004$ ), 0.44 (0.32–0.62,  $P<.00001$ ), and 0.39 (0.22–



**Figure 2.** Risk of bias for eligible randomized controlled trials.

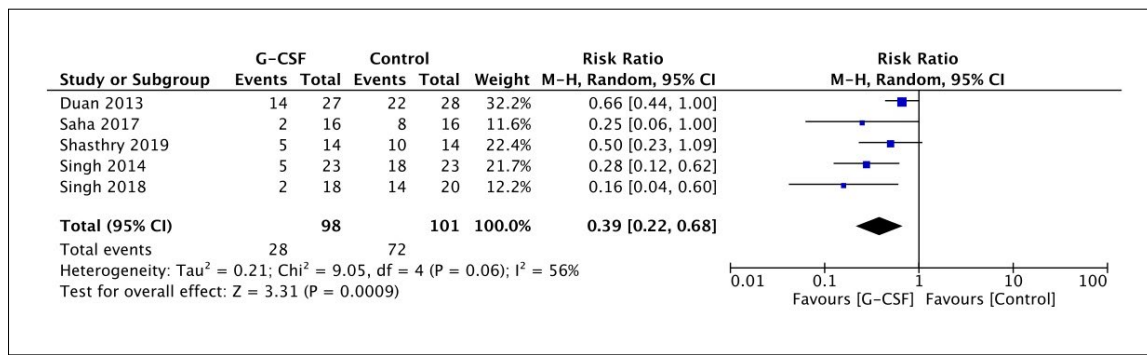
0.68,  $P= 0.0009$ ), respectively, indicating that the administration of G-CSF is probably helpful in increasing the survival rates of patients with ACLF (**Figure 3**).

We performed a subgroup analysis by three different disease states leading to ACLF (severe alcoholic hepatitis,  $n=3$  studies; HBV infection,  $n=1$  study; mixed,  $n=2$  studies). In the first month, the RRs (95% CI,  $P$ ) were 0.41 (0.22–0.78,  $P=.006$ ), 0.52 (0.10–2.60,  $P=.42$ ), and 0.45 (0.21–0.96,  $P=.04$ ) for each of the three states, respectively. In the second month, the values were 0.35 (0.20–0.61,  $P=.0002$ ), 0.55 (0.31–0.95,  $P=.03$ ), and 0.46 (0.25–0.85,  $P=.01$ ), respectively. The RRs for the third month are shown in **Figure 4**. A sensitivity analysis was conducted by deleting individual studies one by one to

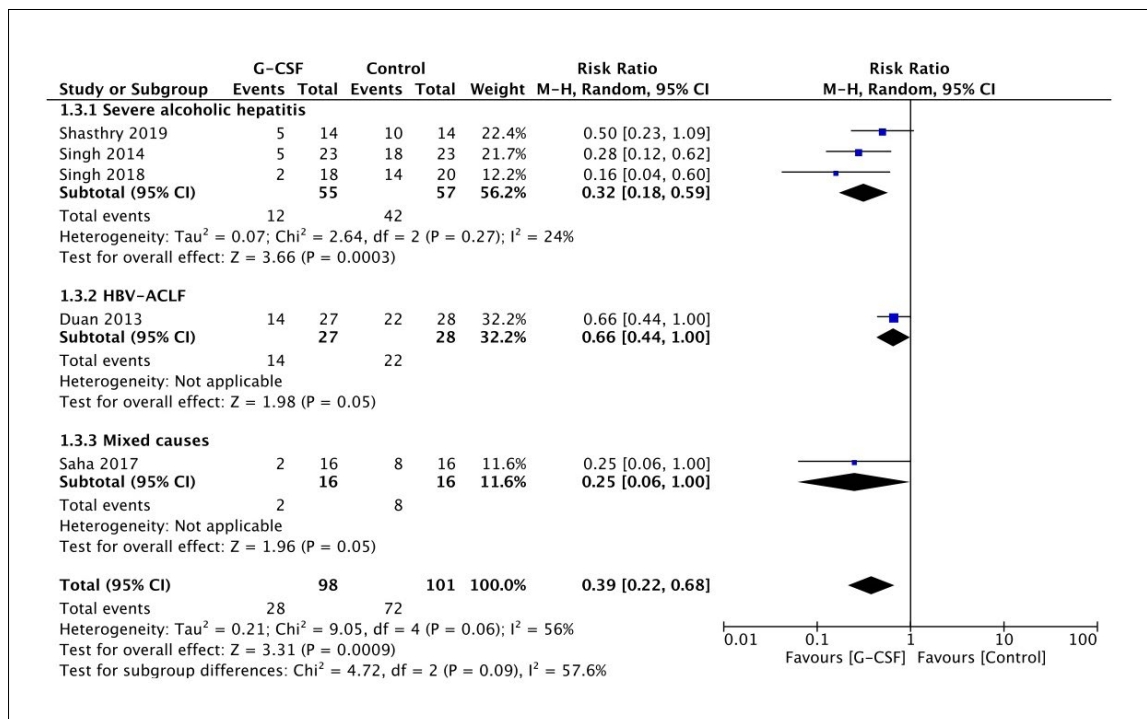
assess the effect on the overall risk ratio and merging the results (**Table 2**). In the analysis of publication bias, no point estimate was outside 95% CI of the meta-analysis in the funnel plot.

**Laboratory results**

In four reports, the baseline counts of all leukocytes were comparable between the experimental and control groups.<sup>10-12,14</sup> G-CSF treatment caused a pronounced improvement in total leukocyte counts on days 3, 6, 15, and 28, compared with baseline values in the four studies. However, no pronounced increase in the total leukocyte count was observed in the control groups. In the four studies that reported the baseline counts,



**Figure 3.** Three-month survival rates in the G-CSF groups vs. control group.



**Figure 4.** Subgroup analysis of three-month survival rates in the G-CSF groups vs. control groups.

peripheral CD34+ cell counts were similar between the treatment groups.<sup>10,12-14</sup> There was a tendency toward improvement in CD34+ cells in the peripheral blood on days 3, 6, and 15 in the G-CSF group when compared with the control controls in the four studies. The CD34+ cell counts were nearly the same in both groups on day 30 in all four studies.

One clinical study reported changes in the hepatic CD34+ cell count, which indicates whether G-CSF stimulates the recruitment and migration of bone marrow-derived cells to the liver in patients with ACLF.<sup>13</sup> The paraffin-embedded tissues were cut into 4- $\mu$ m-thick sections, which were immunohistochemically stained with anti-CD34. The percentage of hepatic CD34+ cells was remarkably increased from baseline to day 30 (27.5% to 40%,  $P=.01$ ) in the G-CSF group, while it decreased (30% to 20%,  $P=.03$ ) in the control group. These changes reflect the fact that bone marrow-derived cells may migrate to the injured hepatic tissue after G-CSF stimulation when ACLF occurs, which might promote hepatic regeneration. At the same time, the number of peripheral CD34+ cells significantly decreased from baseline to day 30 in the G-CSF group, which was probably related to the migration and differentiation of CD34+ cells into hepatic cells under the influence of G-CSF.

#### Adverse reactions

G-CSF was suitable for most clinical patients. The total leukocyte count increased significantly in some patients, as expected, which raises the fear of intercurrent infection. However, the frequency of antibiotic use did not increase. Most investigators also reported patient complaints of rash, headache, bone pain, and fever. However, these symptoms were alleviated by decreasing the frequency and number of doses of G-CSF or by symptomatic treatment; some relieved spontaneously. Singh et al<sup>10</sup> reported an obviously enlarged spleen at

day 5 in the experimental group, but rupture did not occur. There were no reports of allergic reactions or respiratory syndrome.

#### Development of complications and analysis of cause of death

Multiple organ failure and infection are common complications in patients with ACLF. The possibility of hepatic encephalopathy, sepsis, and hepatorenal syndrome was obviously lower in the G-CSF group than in the control group. The infection rates with and without G-CSF were 25% and 32%, respectively. In the experimental group, cases of infection were mostly a single infection, whereas in the control group, the infection was mostly mixed.

## DISCUSSION

Decreasing hepatocyte injury and apoptosis and increasing hepatocyte regeneration are two important aspects of medical treatment strategies for ACLF. Several studies have demonstrated that bone marrow-derived stem cells can be stimulated to migrate and transplant to the injured hepatic tissue by cytokine administration.<sup>16</sup> Patients with chronic liver injury as well as animal models of ACLF have both achieved encouraging results after the use of G-CSF,<sup>17</sup> which justify the clinical use of ACLF with G-CSF. Our meta-analysis further corroborates the benefits of G-CSF treatment with robust integrated evidence. The subgroup analyses showed that G-CSF significantly improved the survival of patients at 1, 2, or 3 months, regardless of the cause of ACLF. Improvements in leukocyte counts occurred in all studies; four studies reported an increase in intrahepatic CD34+ cell counts. G-CSF was likely to prevent severe complications, including sepsis, hepatorenal syndrome, and multiorgan failure. Moreover, no significant adverse events were observed in these clinical studies. All patients with G-CSF died of complications of ACLF

**Table 2.** Sensitivity analysis of merged results before and after exclusion of each study.

Month	Overall effect	Result after exclusion RR (95% CI)					
		Singh, 2018 <sup>10</sup>	Shasthry, 2019 <sup>11</sup>	Singh, 2014 <sup>12</sup>	Grag, 2012 <sup>13</sup>	Duan, 2013 <sup>14</sup>	Saha, 2017 <sup>15</sup>
1-month survival rates	0.43 (0.27-0.69)	0.46 (0.28-0.76)	0.40 (0.24-0.66)	0.46 (0.26-0.79)	0.45 (0.26-0.78)	0.43 (0.26-0.69)	0.42 (0.26-0.68)
2-month survival rates	0.44 (0.32-0.62)	0.47 (0.33-0.66)	0.44 (0.31-0.63)	0.46 (0.32-0.66)	0.45 (0.30-0.66)	0.39 (0.26-0.60)	0.43 (0.31-0.61)
3-month survival rates	0.39 (0.22-0.68)	0.45 (0.28-0.75)	0.34 (0.15-0.73)	0.42 (0.22-0.80)	--	0.32 (0.20-0.52)	0.41 (0.22-0.75)

The risk ratio under each study is the overall risk with that study removed.

rather than any adverse effects of G-CSF. Therefore, we suggest that the progression of multiorgan failure and subsequent death might be prevented by the use of G-CSF.

The mechanism of G-CSF in the treatment of ACLF remains unclear. However, as per the general proposition, G-CSF works by promoting hepatocyte regeneration or by facilitating stem cell migration into the damaged liver, as well as the proliferation and differentiation of stem cells.<sup>18-20</sup> Four studies reported an increase in CD34+ cell counts as a surface marker of hepatic progenitor cells in the peripheral blood or in the hepatic tissue of patients with ACLF at 6 days post-G-CSF administration, compared with the control group.<sup>10,12-14</sup> The randomized trial conducted by Spahr et al<sup>21</sup> also revealed that G-CSF mobilizes and increases the level of CD34+ cells in the blood circulation of patients with alcoholic steatohepatitis. The expression pattern of CXC chemokine receptor 4 (CXCR4), vascular endothelial growth factor receptor (VEGFR), and very late activation antigen 4 (VLA-4) indicate that they all participate in G-CSF-induced stem cell mobilization.<sup>22</sup> Furthermore, autologous CD 34+ cells can effectively improve liver function in a short time,<sup>23,24</sup> which may be a result of increasing settlement and differentiation into hepatic CD34+ cells. Thus, G-CSF may influence hepatic progenitor cell migration from the bone marrow to the liver through the blood circulation, which is demonstrated by the increase in hepatic CD34+ count.<sup>13</sup> Simultaneously, G-CSF may strengthen endogenous hepatic oval cell reactive proliferation.<sup>9,25,26</sup>

G-CSF also participates in regulating inflammatory cytokine signaling pathways. In our pooled analysis, the number of leukocytes increased with use of G-CSF. A main feature of ACLF is a strong and systemic inflammatory response, which is characterized by high plasma C-reactive protein and leukocyte counts, and in some cases, associated mortality.<sup>27</sup> Besides this pro-inflammatory profile, patients with ACLF also display immune paralysis,<sup>28</sup> which can be observed in different etiologies. Neutrophil dysfunction can occur in patients with alcoholic hepatitis overlapping with cirrhosis.<sup>29</sup> A reduction in functional myeloid dendritic cells, which are a key part of the host response against microbes, is observed in HBV-related ACLF and is associated with a poor outcome.<sup>30</sup> G-CSF administration can increase circulating and intrahepatic myeloid dendritic cells, which helps in achieving immune regulation by balancing abnormal immune activation and alleviating any subsequent immune deple-

tion. Immune regulation could facilitate hepatic tissue healing and recovery of function,<sup>31</sup> which might explain why G-CSF is likely to reduce the number of patients experiencing severe complications, such as sepsis.

G-CSF may optimize the efficacy of medical treatment or artificial liver implantation in patients with ACLF. To some extent, prolonging the survival time for patients waiting for an appropriate liver source can also alleviate the problem of organ shortage. From our analysis, the progression and incidence of multiple complications, including multiorgan failure, could be prevented by the use of G-CSF.

Our meta-analysis has some limitations. The overall prognosis of patients with ACLF is poor. The current studies are mostly three months in length; some studies were shorter or longer, but the number is small. The longest follow-up time in those studies that finally met the inclusion and exclusion criteria of this article was only three months. Since we obtained data from published reports instead of having original patient data, the number of included trials and patients is insufficient. All the studies were from countries in Asia, which may limit the external validity of the analysis. However, our analysis effectively summarizes the available data, reaches valid conclusions regarding the efficacy of G-CSF therapy, and provides important insights in the treatment of ACLF. ACLF is characterized by low short-term survival rates, so OLT is the last hope for patients who do not respond to other support therapies. However, the cost is high, and the lack of organs and experienced doctors also makes OLT difficult to implement. G-CSF is beneficial in improving short-term survival rates and liver function in patients with ACLF and is well tolerated. When OLT is unavailable, untimely, or even contraindicated, G-CSF can improve life quality and enhance life expectancy for patients with ACLF. Subsequent liver transplant may be more successful in the G-CSF group, although at present there are no relevant clinical reports on whether G-CSF is beneficial for subsequent liver transplantation. The results of related animal experiments have confirmed that G-CSF can significantly improve the survival rate of the liver after liver transplantation. We may be able to carry out relevant research together with other departments in the future. Those results will bring hope to patients with ACLF. However, before large-scale clinical application, further large-scale clinical studies are needed to assess the outcomes of G-CSF treatment in patients with ACLF worldwide.



**Author contributions**

W.H. and Y.M. contributed to the conceptualization. W.H., Y.M, S.K., and C.L. contributed to the literature collection and screening. L.B. contributed to the judgment if there are some arguments. W.H. contributed to preparation of the original draft. L.D. contributed to the editing. H.T. and X.L. contributed to the supervision.

**REFERENCES**

- Ohnishi H, Sugihara J, Moriwaki H, Muto Y. [Acute-on-chronic liver failure]. *Ryokibetsu Shokogun Shirizu*. 1995(7):217-9.
- Sarin S, Choudhury A, Sharma M, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. *Hepatology international*. 2019;13(4):353-90.
- Blasco-Argora S, Masegosa-Ataz J, Gutierrez-Garcia ML, Alonso-Lopez S, Fernandez-Rodriguez CM. Acute-on-chronic liver failure: Pathogenesis, prognostic factors and management. *World J Gastroenterol*. 2015;21(42):12125-40.
- Lin S, Zhang K, Zhang J, Wang M, Velani B, Zhu Y. Long-term outcomes of patients with hepatitis B virus-related acute on chronic liver failure: An observational cohort study. *Liver Int*. 2019;39(5):854-60.
- Gu J, Shi X, Ren H, Xu Q, Wang J, Xiao J, et al. Systematic review: extracorporeal bio-artificial liver-support system for liver failure. *Hepatology international*. 2012;6(4):670-83.
- Abdallah MA, Waleed M, Bell MG, Nelson M, Wong R, Sundaram V, et al. Systematic review with meta-analysis: liver transplant provides survival benefit in patients with acute on chronic liver failure. *Aliment Pharmacol Ther*. 2020;52(2):222-32.
- Ding BS, Nolan DJ, Butler JM, James D, Babazadeh AO, Rosenwaks Z, et al. Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. *Nature*. 2010;468(7321):310-5.
- Fazel Modares N, Polz R, Haghghi F, Lamertz L, Behnke K, Zhuang Y, et al. IL-6 Trans-signaling Controls Liver Regeneration After Partial Hepatectomy. *Hepatology*. 2019;70(6):2075-91.
- Piscaglia AC, Shupe TD, Oh SH, Gasbarrini A, Petersen BE. Granulocyte-colony stimulating factor promotes liver repair and induces oval cell migration and proliferation in rats. *Gastroenterology*. 2007;133(2):619-31.
- Singh V, Keisham A, Bhalla A, Sharma N, Agarwal R, Sharma R, et al. Efficacy of Granulocyte Colony-Stimulating Factor and N-Acetylcysteine Therapies in Patients With Severe Alcoholic Hepatitis. *Clinical Gastroenterology and Hepatology*. 2018;16(10):1650-6.e2.
- Shashtry S, Sharma M, Shashtry V, Pande A, Sarin S. Efficacy of Granulocyte Colony-stimulating Factor in the Management of Steroid-Nonresponsive Severe Alcoholic Hepatitis: A Double-Blind Randomized Controlled Trial. *Hepatology (Baltimore, Md)*. 2019;70(3):802-11.
- Singh V, Sharma A, Narasimhan R, Bhalla A, Sharma N, Sharma R. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. *The American journal of gastroenterology*. 2014;109(9):1417-23.
- Garg V, Garg H, Khan A, Trehanpati N, Kumar A, Sharma B, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. *Gastroenterology*. 2012;142(3):505-12.e1.
- Duan X, Liu F, Tong J, Yang H, Chen J, Liu X, et al. Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus-associated acute-on-chronic liver failure. *World journal of gastroenterology*. 2013;19(7):1104-10.
- Saha B, Mahtab M, Akbar S, Noor-E-Alam S, Mamun A, Hossain S, et al. Therapeutic implications of granulocyte colony stimulating factor in patients with acute-on-chronic liver failure: increased survival and containment of liver damage. *Hepatology international*. 2017;11(6):540-6.
- Gianni AM, Siena S, Bregni M, Tarella C, Stern AC, Pileri A, et al. Granulocyte-macrophage colony-stimulating factor to harvest circulating haemopoietic stem cells for autotransplantation. *Lancet*. 1989;2(8663):580-5.
- Theocharis SE, Agapitos EB, Margeli AP, Goutas ND, Kittas CN, Davaris PS. Effect of two forms of granulocyte-colony-stimulating factor on hepatic regeneration after 70% partial hepatectomy in rats. *Clin Sci (Lond)*. 1997;92(3):315-20.
- Wang YD, Ma LY, Ji R. [Advances on mechanisms and application of granulocyte colony-stimulating factor in treatment of liver failure]. *Zhonghua Nei Ke Za Zhi*. 2017;56(12):954-7.
- Wan Z, You S, Rong Y, Zhu B, Zhang A, Zang H, et al. CD34+ hematopoietic stem cells mobilization, paralleled with multiple cytokines elevated in patients with HBV-related acute-on-chronic liver failure. *Dig Dis Sci*. 2013;58(2):448-57.
- Kimura M, Yamada T, Iwata H, Sekino T, Shirahashi K, Yoshida N, et al. Preoperative granulocyte-colony stimulating factor (G-CSF) treatment improves congested liver regeneration. *J Surg Res*. 2010;158(1):132-7.
- Spahr L, Lambert JF, Rubbia-Brandt L, Chalandon Y, Frossard JL, Giostra E, et al. Granulocyte-colony stimulating factor induces proliferation of hepatic progenitors in alcoholic steatohepatitis: a randomized trial. *Hepatology*. 2008;48(1):221-9.
- Di Campli C, Zocco MA, Saulnier N, Grieco A, Rapaccini G, Addolorato G, et al. Safety and efficacy profile of G-CSF therapy in patients with acute on chronic liver failure. *Dig Liver Dis*. 2007;39(12):1071-6.
- Sharma M, Rao PN, Sasikala M, Kuncharam MR, Reddy C, Gokak V, et al. Autologous mobilized peripheral blood CD34(+) cell infusion in non-viral decompensated liver cirrhosis. *World J Gastroenterol*. 2015;21(23):7264-71.
- Pai M, Zacharoulis D, Milicevic MN, Helmy S, Jiao LR, Levicar N, et al. Autologous infusion of expanded mobilized adult bone marrow-derived CD34+ cells into patients with alcoholic liver cirrhosis. *Am J Gastroenterol*. 2008;103(8):1952-8.
- Yanagawa T, Sumiyoshi H, Higashi K, Nakao S, Higashiyama R, Fukumitsu H, et al. Identification of a Novel Bone Marrow Cell-Derived Accelerator of Fibrotic Liver Regeneration Through Mobilization of Hepatic Progenitor Cells in Mice. *Stem Cells*. 2019;37(1):89-101.
- Than NN, Newsome PN. Stem cells for liver regeneration. *Qjm*. 2014;107(6):417-21.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(7):1426-37, 37.e1-9.
- Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghoner A, Vidacek D, Siewert E, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. *J Hepatol*. 2005;42(2):195-201.
- Mookerjee RP, Stadlbauer V, Lidder S, Wright GA, Hodges SJ, Davies NA, et al. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology*. 2007;46(3):831-40.
- Zhao J, Zhang JY, Yu HW, He YL, Zhao JJ, Li J, et al. Improved survival ratios correlate with myeloid dendritic cell restoration in acute-on-chronic liver failure patients receiving methylprednisolone therapy. *Cellular & Molecular Immunology*. 2012;9(5):417-22.
- Gustot T. Beneficial role of G-CSF in acute-on-chronic liver failure: effects on liver regeneration, inflammation/immunoparalysis or both? *Liver Int*. 2014;34(4):484-6.