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Original Article

The effects of granulocyte-colony stimulating factor on chronic liver disease: a meta-analysis

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Abstract

Introduction: The clinical application of granulocyte-colony stimulating factor on chronic liver disease is still controversial. The study aimed to evaluate the effects of granulocyte-colony stimulating factor on chronic liver disease.

Methodology: A systematic literature search was performed in PubMed, Embase, Cochrane Library and Chinese Biomedical Literature database. Randomized-controlled trials assessing the efficacy of granulocyte-colony stimulating factor were selected.

Results: Granulocyte-colony stimulating factor was associated with an increasing long-term survival (RR 1.54; 95% CI 1.22 to 1.94; $p = 0.0003$; heterogeneity: Q = 0.26, $I^2 = 25\%$) and an increasing short-term survival (RR 1.44; 95% CI 1.16 to 1.78; $p = 0.0009$; heterogeneity: Q < 0.00001, $I^2 = 80\%$). Granulocyte-colony stimulating factor failed to lower mortality secondary to multiple organ failure (RR 0.65; 95% CI 0.34 to 1.21; $p = 0.17$; heterogeneity: Q = 0.45; $I^2 = 0\%$), gastrointestinal bleeding mortality (RR 0.97; 95% CI 0.61 to 1.56; $p = 0.91$; heterogeneity: Q = 0.35; $I^2 = 11\%$) and sepsis mortality (RR 0.27; 95% CI 0.06 to 1.12; $p = 0.07$; heterogeneity: Q < 0.00001; $I^2 = 90\%$). It significantly lowered the Child-Turcotte-Pugh (MD=−0.97, 95% CI −1.48 to −0.45; $p = 0.0003$; heterogeneity: Q = 0.25; $I^2 = 28\%$). No serious adverse events were observed.

Conclusions: Granulocyte-colony stimulating factor resulted in significantly improved 12-month survival and reduced Child-Turcotte-Pugh score with relative safety. Establishment of guidelines and protocols in future clinical trials will promote granulocyte-colony stimulating factor as an effective and safe therapy for chronic liver disease.

Key words: liver disease; granulocyte-colony stimulating factor; meta-analysis.

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Introduction

Chronic liver disease (CLD), caused by hepatitis viral infection, toxic damage, alcohol abuse, metabolic disorders or genetic defects, is a common clinical condition, which can progress to end stage liver disease (ESLD) if effective treatment is not applied [1].

Although specific therapy of ESLD is deficient, the application of artificial liver and liver transplantation has improved the mortality rate of ESLD to some extent. However, the shortage of plasma, donor liver supply and as well as high cost limit its application. It is vital that we adopt rational and comprehensive medical treatment in the early stage of chronic liver disease. In this context, various innovative therapies based on immune regulation or liver regeneration have been proposed, including the use of granulocyte-colony stimulating factor (G-CSF).

Several studies have suggested G-CSF efficacy in the mobilization and differentiation of bone marrow-derived stem cells [2,3]. G-CSF stimulates autocrine and paracrine in the liver [4]. It also causes proliferation and differentiation of bone marrow precursor cells into mature granulocytes [5,6].

Asian Pacific Association for the Study of the Liver (APASL) Guide, published in 2019, indicates that G-CSF is a promising approach for acute-on-chronic liver failure (ACLF), and its clinical efficacy and safety has been highly recognized [7]. G-CSF is also recommended for end stage liver disease complicated with infections and liver failure according to expert consensus of China [8]. However, this is not recommended by the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines [9]. Therefore, the application of G-CSF in the treatment of liver disease is still controversial. Some relevant high-quality randomized control trials (RCTs) have been published recently. We performed an update

to the meta-analysis of trials and provided a reference guide for clinical decision.

Methodology

We conducted a meta-analysis in conformity with the Cochrane Handbook [10] and reported the findings in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11]. The protocol is registered on PROSPERO (CRD42021227293).

PICO question

In human subjects, does G-CSF therapy bring survival benefits compared to standard medical therapy (SMT) [P: patients diagnosed with chronic liver disease; I: use of G-CSF alone or in combination; C: standard medical therapy (SMT) alone or in combination with placebo; O: primary outcomes: survival, mortality secondary to multi-organ failure, mortality secondary to gastrointestinal bleeding, mortality secondary to sepsis, occurrence rate of infection, adverse events. Secondary outcomes: Child-Turcotte-Pugh (CTP) score, end-stage liver disease (MELD) score, changes in peripheral CD34+ cell count].

Search strategy and study selection

We performed a systematic study selection through four databases [PubMed, Embase, Cochrane Library, CBM (Chinese Biomedical Literature database)] from inception to December 2020. The reference lists of the retrieved studies were also checked for relevant studies. Combinations of medical subject heading (MeSH) and keywords were used: ("liver disease" or "hepatitis" or "hepatic fibrosis" or "liver fibrosis" or "liver cirrhosis" or "liver neoplasm" or "liver failure" or "fatty liver" or "liver abscess" or "liver injury") and ("granulocyte colony-stimulating factor" or "G-CSF" or "rhG-CSF" or "r-metHuG-CSF"). The search strategy was limited to human subjects but without restriction on language. We tried to contact the authors if we could not obtain the full text of an article. Two reviewers (Pei Shi and Jianguo Zhang) screened and examined literature independently and discussed with a third reviewer (Xiaoping Wu) in case of disagreement.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients diagnosed with CLD; (2) randomized-controlled trials (RCTs); (3) patients in the experimental group received G-CSF therapy and patients in the control group were treated with SMT; (4) reported at least survival rates in patients with CLD before and after G-CSF therapy.

The following trials were excluded: (1) insufficient or unusable data; (2) letters, comments, case reports and review articles. When duplicate reports were identified, only the most recent was taken into account.

Data extraction

Two reviewers (Pei Shi and Jianguo Zhang) extracted data from eligible studies independently, and resolved the disagreements by discussion with a third reviewer (Xiaoping Wu). The following data were recorded from the eligible studies: study characteristics (first author, publication year, country, study design), patient characteristics (age, sex, and liver disease etiology), dosage of G-CSF, times of injection, duration of follow-up and outcome measures (primary outcomes: survival, mortality secondary to multi-organ failure, mortality secondary to gastrointestinal bleeding, mortality secondary to sepsis, occurrence rate of infection, adverse events. Secondary outcomes: CTP score, MELD score, changes in peripheral CD34+ cell count).

Risk of bias for the included studies

Cochrane Collaboration's Risk of Bias tool [12] was used to assess the quality of randomized-controlled trials, which measures quality in selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), measurement bias (blinding of outcome assessment), reporting bias (selective outcome reporting), and other bias. Two reviewers (Pei Shi and Jianguo Zhang) made independent judgment of low risk of bias and high risk of bias or unclear for each project and any disagreements were resolved by discussion and consulting with a third reviewer (Xiaoping Wu).

Statistical analysis

For RCTs, dichotomous variables were evaluated by risk ratio (RR) with 95% confidence interval (CI), continuous variables, including CTP Score and MELD Score, were evaluated by mean difference (MD) while peripheral CD34+ cell count was evaluated using standardized mean difference (SMD). p value < 0.05 was considered to be statistically significant. Statistical heterogeneity among the studies was evaluated by the Cochran's Q test ($p < 0.10$ was deemed as significant heterogeneity) and I^2 statistic ($I^2 > 50\%$ indicated significant heterogeneity). In the absence of significant heterogeneity, we used fixed-effects models; otherwise,

we used random-effects models. Publication bias was explored by funnel plot. The statistical package Review Manager version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for all data analyses.

Results

Study selection

Eligible studies were RCTs that investigated granulocyte-colony stimulating factor for liver failure in both pediatric and adult patients regardless of liver disease etiology. Our study search yielded 1032 records from four database and manual searching of the reference lists, of which 139 repetitive records were removed and 715 literatures were further excluded after titles and abstracts were screened. 178 studies remained and were checked in detail. 161 of these studies were excluded, 24 of which were reviews and meta-analyses, 27 were letters, comments and case reports, 54 had no comparative studies, and 73 reported insufficient or unusable data. Finally, after detailed review of the full texts, 17 studies [13-29] were included in quantitative synthesis (Figure 1).

Study characteristics

The characteristics of the literature are presented in Table 1. All 17 studies were RCTs, published between 2008 and 2020 and came from India (n = 10), China (n = 3), Bangladesh (n = 1), Switzerland (n = 1), the United Kingdom (n = 1) and multicenter countries in Europe (n = 1). In total, 1167 patients were included, 581 patients receiving G-CSF therapy, and 586 patients receiving standard medical therapy. These studies included patients with ACLF (n = 6), alcoholic liver disease (n = 6) and liver cirrhosis (n = 5). One trial focused on children with liver failure (aged > 1 year) [17], 3 trials focused on the use of multiple cycles of G-CSF [17,20,23] and 1 trial focused on the use of recombinant granulocyte colony-stimulating factor (rG-CSF) [19].

Quality assessment and publication bias

The quality assessment of each study is presented in Figure 2. The risk of bias for the 17 selected studies was low or moderate. Publication bias was explored by funnel plot (Figure 3).

Table 1. Characteristics of included studies.

Study	Year	Country	Disease	Sample size	Average age (years)	Male (%)	Dosage of G-CSF	Follow-up (months)
Garg [13]	2012	India	ACLF	23/24	40/40	87.0%/87.5%	5μg/kg/dose 12 doses	2
Duan [14]	2013	China	ACLF (HBV associated)	27/28	43.5/45.9	81.5%/78.6%	5μg/kg/dose 6 doses	3
Prajapati [15]	2017	India	Decompensated cirrhosis	126/127	53/55	85%/82%	5μg/kg/dose 10 doses	6
De [16]	2020	India	Decompensated cirrhosis	50/50	50.85/48.71	86%/84%	5μg/kg/dose 10 doses for 4 cycles	12
Sharma [17]	2019	India	ACLF	15/16	7.53/6.31	46.7%/75%	5μg/kg/dose 6 doses	2
Saha [18]	2017	Bangladesh	ACLF	16/16	39/48	75%/100%	5μg/kg/dose 6 doses	3
Xu [19]	2016	China	ACLF (HBV associated)	49/50	41.72/45.62	83.33%/84%	300μg/kg/dose 12 doses	3
Verma [20]	2018	India	Decompensated cirrhosis	21/21	52.6/50.5	85.7%/66.7%	5μg/kg/dose 10 doses for 4 cycles	12
Newsome [21]	2018	UK	Compensated cirrhosis	27/26	52/54	48%/69%	15μg/kg/dose 5 doses	3
Engelmann [22]	2019	Multicentric, Europe	ACLF	81/82	54.2/56.9	57%/68%	5μg/kg/dose 12 doses	3
Venkitaraman [23]	2020	India	Decompensated cirrhosis	35/35	Not reported	Not reported	5μg/kg/dose 10 doses for 4 cycles	12
Spahr [24]	2008	Switzerland	Alcoholic steatohepatitis	13/11	53.2/54.5	85%/54%	10μg/kg/dose 5 doses	3
Singh [25]	2014	India	Severe alcoholic hepatitis	23/23	41.7/44.3	100%/100%	10μg/kg/dose 5 doses	3
Singh [26]	2018	India	Severe alcoholic hepatitis	18/20	41.6/44.7	100%/100%	10μg/kg/dose 5 doses	3
Sharmal [27]	2017	India	Severe alcoholic hepatitis	25/25	49.4/48.6	100%/100%	5μg/kg/dose 5 doses	3
Shasthry [28]	2019	India	Severe alcoholic hepatitis	14/14	39.6/40.7	96%	5μg/kg/dose 12 doses	3
Zhou [29]	2020	China	End-stage alcoholic liver disease	18/18	18-75	100%/100%	5μg/kg/dose 14 doses	3

Figure 1. Flow diagram of the selection of literatures.

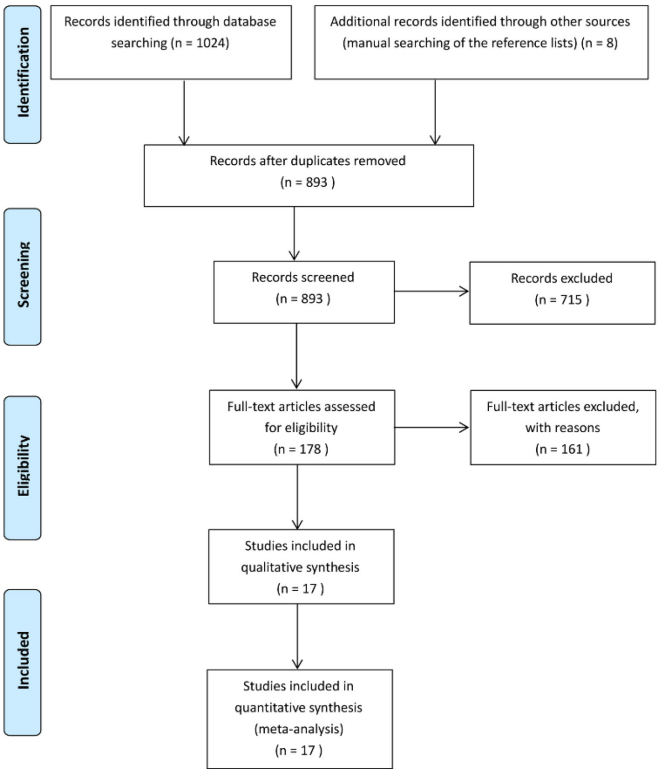


Figure 2. Quality assessment of studies included. + is "low risk of bias", - is "high risk of bias"? is "unclear risk of bias".

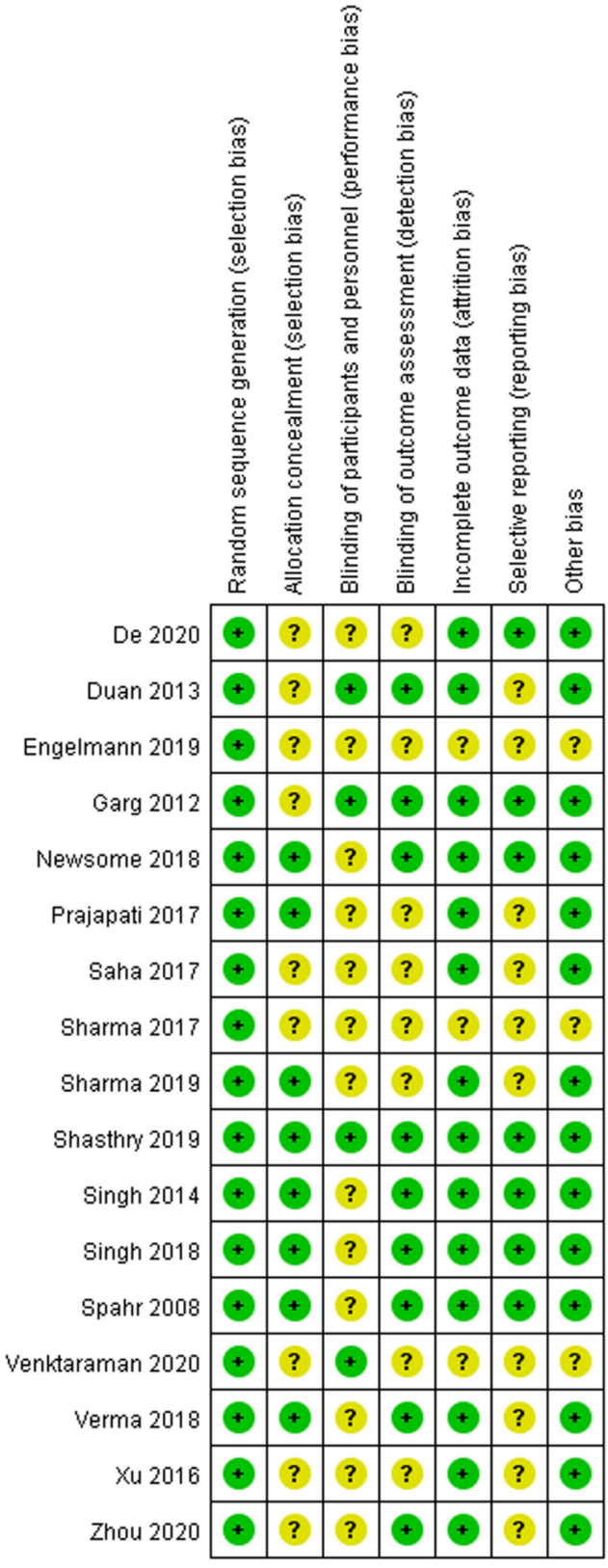
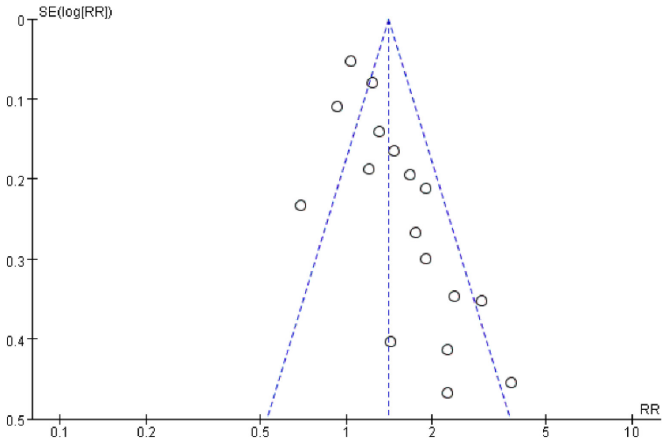


Figure 3. Funnel plot to evaluate potential publication bias.



Results of the quantitative analysis

Survival rate

All seventeen trials [13-29] reported survival from 2 to 12 months. In overall meta-analysis, G-CSF therapy was associated with an improved survival (RR 1.46; 95% CI 1.21 to 1.76; $p < 0.0001$). There was high heterogeneity between studies (Q < 0.001; I^2 =79%) (Figure 4). In the subgroup analysis of long-term survival (12-month), G-CSF therapy was associated with an increased survival rate compared with SMT group (RR 1.54; 95% CI 1. 22 to 1.94; $p = 0.0003$), no heterogeneity (Q = 0.26; I^2 = 25%). In the short-term survival (6 months or less) subgroup analysis, there was still substantial heterogeneity among studies (Q < 0.00001; I^2 = 80%). Further, the included studies were divided into ACLF group, alcoholic liver disease group and liver cirrhosis group for subgroup analysis. There was heterogeneity among studies in ACLF group (Q = 0.02; I^2 = 63%). By excluding one study in Europe [22], sensitivity analyses showed that the heterogeneity among the remaining Asian studies was eliminated. G-CSF therapy was associated with an increased survival rate in Asian ACLF patients (OR = 0.72; 95% CI 1.35 to 2.18; $p < 0.00001$) with no heterogeneity (Q = 0.66;

Figure 4. Pooled estimate rate for survival during follow-up. (a) survival rate at the final follow-up, (b) short-term survival (6 months or less), (c) long-term survival (12-month).

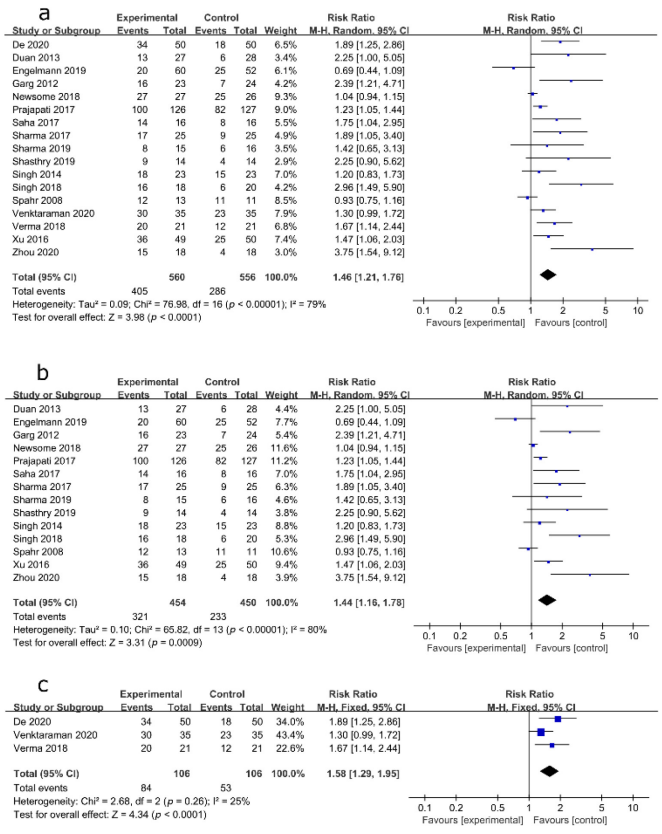


Figure 5. Pooled estimate rate for survival among patients with ACLF. Treated by (a) G-CSF and controls in Asian and European studies, (b) G-CSF and controls in Asian studies.

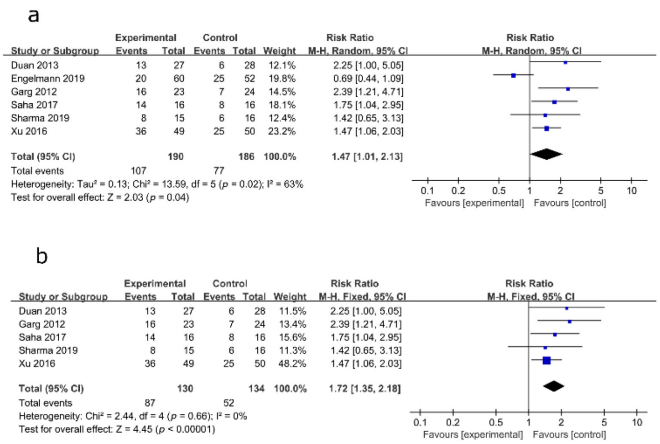


Figure 6. Pooled estimate rate for survival among patients with alcoholic liver disease. Treated by (a) G-CSF and controls for non-severe and severe alcoholic liver disease, (b) G-CSF and controls for severe alcoholic liver disease.

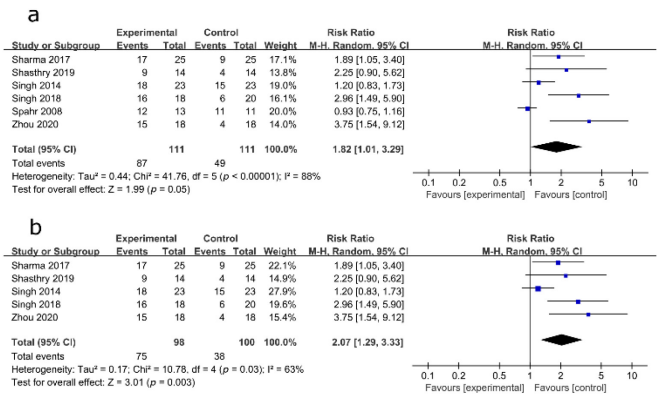
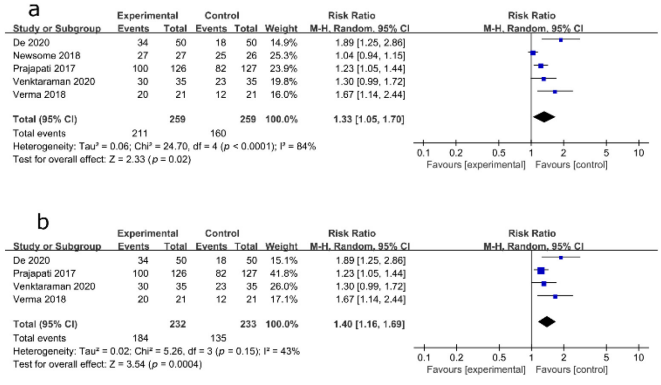


Figure 7. Pooled estimate rate for survival among patients with liver cirrhosis. Treated by (a) G-CSF and controls for compensated and decompensated cirrhosis, (b) G-CSF and controls for decompensated cirrhosis.

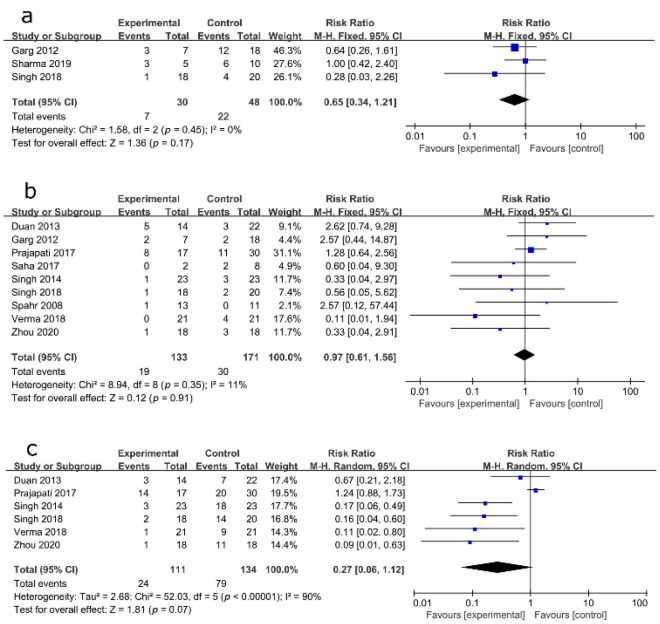


I^2 = 0%) (Figure 5). We found high heterogeneity among studies of alcoholic liver disease (Q < 0.00001; I^2 = 88%). By excluding one study of non-severe alcoholic liver disease [24], sensitivity analyses showed lowered heterogeneity among the remaining studies (Q = 0.03; I^2 = 63%) (Figure 6). There was substantial heterogeneity among studies of liver cirrhosis (Q < 0.0001; I^2 = 84%). One study included patients with compensated cirrhosis [21], in a sensitivity analysis excluding this study, the heterogeneity among the remaining studies was lowered (Q = 0.15; I^2 = 43%) (Figure 7). These results were similar to those of overall analyses.

Mortality secondary to complications

Three trials [13,17,26] reported mortality secondary to multi-organ failure. There was no statistically significant difference for the G-CSF group and the SMT group to observed (RR 0.65; 95% CI 0.34 to 1.21; p = 0.17) with no heterogeneity (Q = 0.45; I^2 = 0%). Nine trials [13-15,18,20,24-26,29] reported gastrointestinal bleeding as cause of death. It was not statistically different (RR 0.97; 95% CI 0.61 to 1.56; p = 0.91) with no heterogeneity between studies (Q = 0.35; I^2 = 11%). Six trials [14,15,20,25,26,29] reported sepsis mortality. G-CSF therapy was not associated with a reduced sepsis mortality compared to controls (RR 0.27; 95% CI 0.06 to 1.12; p = 0.07) with high heterogeneity between studies (Q < 0.00001; I^2 = 90%) (Figure 8).

Figure 8. Pooled estimate of mortality secondary to complications. (a) mortality secondary to multi-organ failure, (b) mortality secondary to gastrointestinal bleeding, (c) mortality secondary to sepsis.



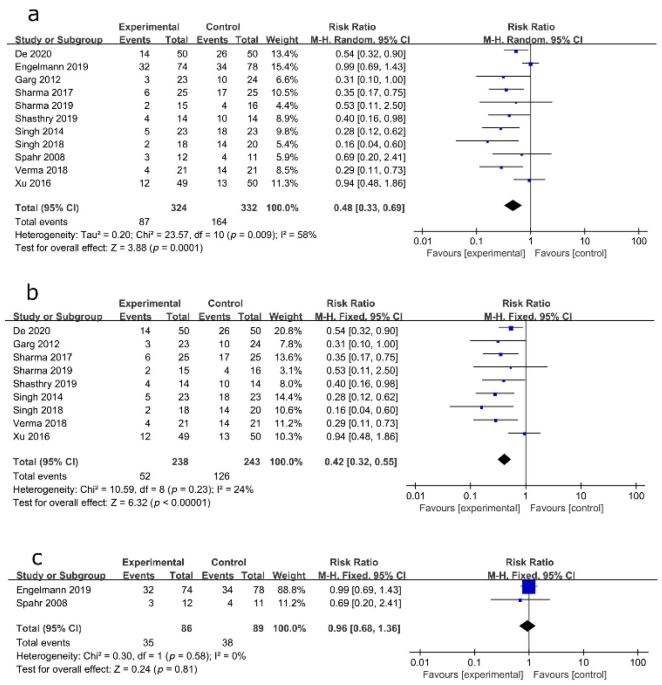
Occurrence rate of infection

Eleven trials [13,16,17,19,20,22,24-28] reported the infection occurrence rate. In overall meta-analysis, G-CSF therapy showed a reduced occurrence rate of infection than SMT (RR 0.48; 95% CI 0.33 to 0.69; p = 0.0001). There was high heterogeneity between studies (Q = 0.009; I^2 = 58%). In Asian studies, risk of developing infections was lower in G-CSF patients than in controls (RR 0.42; 95% CI 0.32 to 0.55; p < 0.00001) with no heterogeneity (Q = 0.23; I^2 = 24%), while in European studies, occurrence of infection was not statistically different (RR 0.96; 95% CI 0.68 to 1.36; p = 0.81) with no heterogeneity (Q = 0.58; I^2 = 0%) (Figure 9).

Child-Turcotte-Pugh score

Eleven trials [13-18,20,21,25,26,28] reported CTP score during the follow-up period. Seven trials [13,15,16,20,21,25,26] reported the outcome measure as the median change. Among them, in five studies [13,15,16,20,25], the reduction of CTP score was observed after G-CSF therapy compared with SMT. While the Newsome study [21] and the Singh study [26] showed G-CSF therapy was not associated with a reduced CTP score compared to controls. The pooled estimates of four trials [14,17,18,28] showed that G-CSF therapy significantly lowered the CTP score from

Figure 9. Pooled estimate of the occurrence rate of infection. Treated by (a) G-CSF and controls in Asian and European studies, (b) G-CSF and controls in Asian studies, and (c) G-CSF and controls in European studies.



baseline after G-CSF treatment compared with the SMT group which was statistically different (MD = −0.97, 95% CI −1.48 to −0.45; $p = 0.0003$; heterogeneity: Q = 0.25; $I^2 = 28\%$) (Figure 10).

MELD score

Eleven studies [13,14,16,18-21,25,26,28,29] reported MELD score from baseline to the end of follow-up. Seven studies [13,16,20,21,25,26,29] described the outcome as the median change and six studies [13,16,20, 25,26,29] showed that there were significantly low MELD scores after G-CSF therapy, but Newsome study [21] showed no difference in change in MELD score at 90-day between G-CSF group and SMT group. A meta-analysis of Duan, Saha, Xu and Shasthry studies [14,18,19,28] reported that G-CSF treatment did not result in a more significant decrease in MELD score (MD = −2.18, 95% CI −7.57 to 3.20; $p = 0.43$). High heterogeneity was detected between studies (Q < 0.0001; $I^2 = 93\%$). Hence, a random-effects model was performed (Figure 11).

Peripheral CD34+ cell count

Eleven trials [13-17,20,21,24-26,29] reported the peripheral CD34+ cell count at week-1. Six studies [13,15,16,20,21,24] reported peripheral CD34+ cell count as median change. These results revealed CD34+ cells were increased significantly in the G-CSF group than in the SMT group. A meta-analysis of five studies [14,17,25,26,29] reported that the magnitude of the increase in the peripheral CD34+ cell count was greater in the G-CSF group compared with the control group (SMD = 2.35; 95% CI 0.87 to 3.83; $p = 0.002$). High heterogeneity was detected between studies (Q < 0.0001; $I^2 = 94\%$). Hence, a random-effects model was performed (Figure 12).

Adverse events

Eleven (13,14,16,17,19,20,23-26,29) studies reported that they were well tolerated with no discontinuation of G-CSF therapy, minor adverse events were mostly self-limiting, including fever, rash, back pain, bone pain, headache, nausea, fatigue, herpes zoster. One study [28] reported one patient developed severe bone pains with every injection of G-CSF, which necessitated decreasing the frequency and the number of doses of G-CSF. Three studies [21,22,27] showed no statistically significant difference in the incidence of adverse events between G-CSF therapy and SMT.

Figure 10. Pooled estimate of Child-Turcotte-Pugh score.

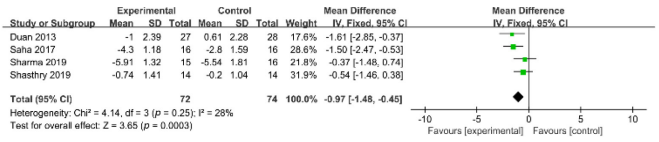


Figure 11. Pooled estimate of MELD score.

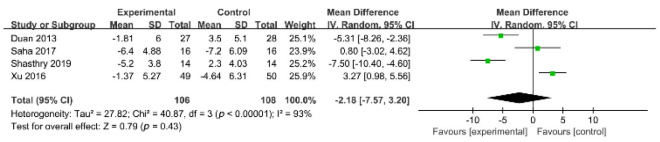
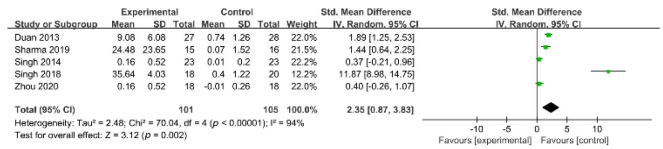


Figure 12. Pooled estimate of peripheral CD34+ cell count.



Discussion

The meta-analysis was aimed at evaluating the survival benefit and biochemical functions of granulocyte-colony stimulating factor in patients with liver disease. G-CSF therapy was associated with long-term survival (12-month) improvement compared with SMT, with no heterogeneity. G-CSF therapy was also associated with an increasing short-term survival (6 months or less) but there was high heterogeneity between the studies. In the subgroup analysis of ACLF, alcoholic liver disease and liver cirrhosis, there was still substantial heterogeneity among studies. In sensitivity analyses, excluding studies that included ACLF patients in Europe, patients with non-severe alcoholic liver disease, or patients with compensated cirrhosis, the heterogeneity was decreased significantly and results were similar to those of overall analyses. There were no significant differences for mortality secondary to complications, including multi-organ failure, gastrointestinal bleeding and sepsis. In the aspect of occurrence of infection, conflicting results between the Asian and European studies were observed. G-CSF therapy significantly lowered the CTP score but MELD scores were not significantly decreased compared with SMT. G-CSF therapy significantly increased peripheral CD34+ cell than SMT. Additionally, no serious adverse events associated with G-CSF therapy was observed.

Previously one meta-analysis [30] that included two Asian trials, demonstrated that the use of G-CSF significantly reduced short-term mortality in patients with ACLF and failed to reduce mortality secondary to

gastrointestinal bleeding. Our study included five trials on ACLF patients, and suggested that G-CSF therapy was associated with an increased survival rate in Asian ACLF patients. No significant differences in mortality secondary to complications, including multi-organ failure, gastrointestinal bleeding and sepsis were observed. Recently two meta-analyses [31,32] have clarified the effect of G-CSF on alcoholic hepatitis. Baig *et al.* [31] proved the efficacy in improving 90-day survival and liver severity indices (Child-Turcotte-Pugh, MELD, and Maddrey discriminant function) after 28 days of treatment. Marot *et al.* [32] showed opposite results in Asian studies and European studies, both for mortality and rate of infection. Our study included six trials on alcoholic liver disease and demonstrated that G-CSF therapy was associated with an improvement in survival, but there was heterogeneity.

The main mechanism of G-CSF in the treatment of liver failure remains controversial. To summarize, the possible mechanism in currently available studies is as follows: (1) G-CSF can mobilize and attract bone marrow hematopoietic stem cells to colonize in the damaged liver, promoting hepatic regeneration [33-40], on the one hand, bone marrow hematopoietic stem cells directly differentiate into liver cells to participate in tissue repair [24,41]. On the other hand, bone marrow hematopoietic stem cells may secrete some factors or signals by paracrine way, stimulate and enhance the reactive proliferation of endogenous liver oval cells (liver stem cells), and initiate endogenous repair procedures [4]; (2) G-CSF inhibits hepatocytes apoptosis/necrosis and plays an important role in immune modulation to protect injured liver [42]; (3) G-CSF increases, activates neutrophil and corrects neutrophil defect, restores the impaired immune system in liver failure, thereby preventing sepsis, and reducing mortality [43,44].

As far as we know, there were several systematic reviews and meta-analyses on G-CSF treating cancer patients after chemotherapy. This meta- analysis updated the evidence-based research in the field of liver disease. Admittedly, our meta-analysis has imperfections. Firstly, the number of trials for various etiologies of chronic liver diseases was relatively limited, it was not conducive to perform a subgroup analysis. Secondly, there is an imbalance between the regions of the included studies, as the majority of them came from Asia [13-20,23,25-29]. Thirdly, few trials have reported complete outcome measures at the various follow-up time points and some outcome indicators were shown as median and respective ranges, so there was limited data for us to do the pooled estimate. But we assessed heterogeneity and risk of bias, under the limited conditions, using pooled results in a meta-analysis.

Conclusions

As an immunological adjuster, G-CSF therapy brought survival benefit to liver disease patients and reduced Child-Turcotte-Pugh score with relative safety. Conflicting results between the Asian and European studies were observed in the aspect of occurrence of infection. There is certainly a need for further large-scale and high-quality studies.

Acknowledgements

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