

Therapeutic Effect of Granulocyte Colony-Stimulating Factor Therapy In Acute-On-Chronic Liver Failure: A Meta-Analysis of Randomized Controlled Trials

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Background

- Acute-on-chronic liver failure (ACLF) is a condition characterized by acute decompensation of chronic liver disease, accompanied by the failure of one or more extrahepatic organs and high short-term mortality.
- Currently, liver transplantation is the only definitive treatment for ACLF but it is not available to all patients due to limited donors, expensive procedure and high risk of adverse effects. Granulocyte stimulating factor (G-CSF) could be considered as an alternative treatment.
- However, its therapeutic effectiveness is still debatable, so we aimed to conduct a meta-analysis to evaluate the clinical efficacy of G-CSF In patients with ACLF.

Methods

- MEDLINE and SCOPUS were queried from inception till June 2022 for randomized controlled trials (RCTs), without any restriction.
- RCTs evaluating effects of G-CSF on survival rates and occurrence of infection in patients with ACLF were incorporated.
- The results were reported using a random-effects metaanalysis and the Mantel-Haenszel risk ratio (RR). The Subgroup analysis was done to investigate the influence of study-level factors such as study setting, population and etiology on the outcomes of interest.

Figure1: Survival rates in patients with alcoholic hepatitis and viral hepatitis

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Duan et al. 2013	13	27	6	28	4.8%	2.25 [1.00, 5.05]	-
Engelmann et al. 2019	20	60	25	52	9.4%	0.69 [0.44, 1.09]	
Engelmann et al. 2021	27	88	26	88	9.5%	1.04 [0.66, 1.63]	+
Garg et al. 2012	16	23	7	24	6.1%	2.39 [1.21, 4.71]	
Haque et al. 2020	8	22	5	17	4.0%	1.24 [0.49, 3.10]	- •
Saha et al. 2017	14	16	8	16	8.2%	1.75 [1.04, 2.95]	
Sharma et al. 2019	8	15	6	16	5.0%	1.42 [0.65, 3.13]	 • •
Shasthry et al. 2019	9	14	4	14	4.0%	2.25 [0.90, 5.62]	+
Singh et al. 2014	18	23	5	23	4.9%	3.60 [1.61, 8.05]	
Singh et al. 2018	16	18	6	20	6.0%	2.96 [1.49, 5.90]	
Tong et al. 2022	36	54	30	57	12.2%	1.27 [0.93, 1.73]	
Xiang et al. 2016	45	49	32	50	14.0%	1.43 [1.15, 1.80]	-
Xu et al. 2016	36	49	25	50	11.9%	1.47 [1.06, 2.03]	-
Total (95% CI)		458		455	100.0%	1.52 [1.23, 1.88]	•
Total events	266		185				
Heterogeneity: Tau ² = 0.0	07; Chi² = 2	8.59, df	= 12 (P =	0.009); l² = 55%	, 6	0.04 0.4 4.0 4.00
Test for overall effect: Z =	3.88 (P =	0.0001)	·				0.01 0.1 1 10 100 Favours [G-CSF] Favours [control]

Figure 2: Survival rates in patients with viral hepatitis

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Duan et al. 2013	13	27	6	28	3.0%	2.25 [1.00, 5.05]	
Garg et al. 2012	16	23	7	24	4.3%	2.39 [1.21, 4.71]	
Haque et al. 2020	8	22	5	17	2.4%	1.24 [0.49, 3.10]	
Saha et al. 2017	14	16	8	16	7.3%	1.75 [1.04, 2.95]	
Sharma et al. 2019	8	15	6	15	3.3%	1.33 [0.61, 2.91]	- •
Tong et al. 2022	36	54	30	57	20.8%	1.27 [0.93, 1.73]	+
Xiang et al. 2016	45	49	32	50	39.9%	1.43 [1.15, 1.80]	-
Xu et al. 2016	36	49	25	50	19.0%	1.47 [1.06, 2.03]	-
Total (95% CI)		255		257	100.0%	1.47 [1.27, 1.69]	•
Total events	176		119				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.66$, $df = 7$ ($P = 0.70$); $I^2 = 0\%$							04 04 4 40 400
Test for overall effect: $Z = 5.32$ (P < 0.00001)							.01 0.1 1 10 100 Favours [G-CSF] Favours [control]

Figure 3: Survival rates in patients with alcoholic hepatitis

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Engelmann et al. 2019	20	60	25	52	22.6%	0.69 [0.44, 1.09]	-
Engelmann et al. 2021	27	88	26	88	22.7%	1.04 [0.66, 1.63]	-
Shasthry et al. 2019	9	14	4	14	16.8%	2.25 [0.90, 5.62]	
Singh et al. 2014	18	23	5	23	18.2%	3.60 [1.61, 8.05]	
Singh et al. 2018	16	18	6	20	19.7%	2.96 [1.49, 5.90]	_
Total (95% CI)		203		197	100.0%	1.66 [0.88, 3.16]	
Total events	90		66				
Heterogeneity: Tau² = 0.4			= 4 (P = I	0.0003); I²= 819	Ó	0.01 0.1 1 10 100
Test for overall effect: $Z = 1.56$ (P = 0.12)							Favours [G-CSF] Favours [control]

Results

- Thirteen studies (n = 13) were included in our metaanalysis. The total number of participants in our study was 913, and the median study duration was 3 months.
- Our pooled analysis demonstrates that G-CSF therapy significantly improved survival rates (RR 1.52; 95% Cl 1.23 to 1.88; p = 0.0001; Figure 1) in patients with ACLD. In our subgroup analysis,
- G-CSF was not found to be associated with an improved survival rate in patients with alcoholic hepatitis (RR 1.47; 95% Cl 1.27 to 1.69; p <0.00001, Figure 2). Similar results for patients with alcoholic hepatitis were not statistically significant (RR 1.66; 95% Cl 0.88 to 3.16; p< 0.12; Figure 3).

CONCLUSIONS

 Our findings indicate that G-CSF therapy is not beneficial in improving survival rates and does reducing the risk of infection in patients with ACLF.