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G-CSF—In Patients With Severe Alcohol-Associated Hepatitis: A Real-World Experience

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ABSTRACT

Background and Aims: Severe alcohol-associated hepatitis (SAH) is associated with high short-term mortality, and failure of response to corticosteroids is associated with a mortality of ~70%–80% within 6 months. Granulocyte colony-stimulating factor (G-CSF) has been studied in steroid non-responders; however, the data are limited.

Methods: This is a multicentre retrospective cohort study. The study period was from January 2016 to November 2023. SAH was defined as alcohol-associated hepatitis (ICD-10-CM codes) with serum bilirubin ≥ 5.0 mg/dL and INR ≥ 1.5. Other aetiologies of acute hepatitis and biliary obstruction were excluded. The primary outcome was 90-day median overall survival in SAH patients treated with G-CSF compared with standard medical therapy (SMT) or corticosteroids. Propensity score (1:1) matching was performed to control confounding variables.

Results: Among 20 132 patients with SAH, 10800 (53.65%) were treated with corticosteroids and 224 (1.11%) G-CSF. The G-CSF group was younger (45.5 vs. 48.4) White (79.91% vs. 72.40%); however, there was no age or gender difference between G-CSF and corticosteroid groups. Whites and patients with more comorbidities received G-CSF more frequently than SMT or corticosteroids. After propensity score matching, 90-day overall survival was better in patients who received G-CSF (88.31% vs. 62.36%, $p < 0.01$) compared with SMT or corticosteroids (88.31% vs. 74.39%, $p < 0.01$). Patients on G-CSF had better 6-month transplant-free survival compared with SMT (83.53% vs. 55.36%, $p < 0.001$) or corticosteroids (82.89% vs. 60.21%, $p < 0.001$). Gastrointestinal bleeding was less common in G-CSF group compared with corticosteroids (5.02% vs. 10.50%, $p < 0.001$).

Conclusions: A small minority of patients with severe alcohol-associated hepatitis receive G-CSF. G-CSF improves 90-day overall survival in patients with severe alcohol-associated hepatitis and is non-inferior to corticosteroids.

1 | Background

Severe alcohol-associated hepatitis (SAH) portends a poor prognosis and carries a high short-term mortality. In the absence of treatment, 30%–50% of patients with SAH succumb to their illness within the first month of presentation [1–3]. Corticosteroids are the mainstay of treatment and multiple clinical trials have demonstrated their survival advantage over placebo [2, 4]. However, despite corticosteroid treatment 28-day mortality is greater than 15%–20%, but can be as high as 40%, and the survival benefit tends to wane over time [5–7]. Moreover, a significant proportion of patients with SAH are not candidates for

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; ICD-10-CM, international classification of diseases, 10th revision, clinical modification; INR, international normalised ratio; MELD, model for end-stage liver disease; RR, risk ratio; SAH, severe alcohol-associated hepatitis; SMT, standard medical therapy

Summary

- Severe alcohol-associated hepatitis is associated with high short-term mortality without transplant and corticosteroids are the only recommended treatment.
- Corticosteroids remain the mainstay of treatment for alcohol-associated hepatitis and use of G-CSF is limited.
- Our study indicates potential role of G-CSF in patients with severe alcohol-associated hepatitis with likely improvement in 90-day overall survival and 6-month transplant-free survival compared with standard medical therapy.

corticosteroids due to contraindications, like—uncontrolled infection, gastrointestinal bleeding or acute kidney injury.

Severe liver inflammation leads to hepatocyte necrosis and along with the systemic inflammatory response impedes liver cell regeneration. While corticosteroids function by attenuating the inflammatory response, an important therapeutic target is augmenting hepatic regeneration. Granulocyte colony-stimulating factor (G-CSF) mobilises $CD34^+$ cells, induces hepatocyte growth factor and stimulates proliferation of hepatocyte progenitor cells [8–10]. G-CSF has demonstrated efficacy in promoting hepatic regeneration in translational studies and has shown promise in clinical trials at improving survival of patients with SAH [9–12]. However, most of these studies are small scale and are from Asia.

In a large clinical trial on the use of G-CSF in patients with acute-on-chronic liver failure, Engelman et al., did not find any significant benefit of G-CSF over standard medical therapy in improving 90-day transplant-free survival [13]. Alcohol-associated hepatitis comprised about half of all the precipitating events in both the study cohorts. While this is the only well powered study aimed to investigate patients with acute-on-chronic liver failure, only one third of the entire G-CSF arm completed the planned number of doses and the survival data in patients with alcohol-associated hepatitis is unavailable. Thus, there is inadequate data to support or refute the use of G-CSF in SAH.

2 | Methods

2.1 | Study Setting and Database

This is a multicentre retrospective cohort study using a large research network (TriNetX, LLC) comprising over 100 million patients. 'TriNetX is the global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) across large healthcare organizations'. The network research with 89 health-care organisations was queried on May 2, 2024, and all the 89 health-care organisations comprising approximately 109 million patients responded. The network research obtains data from electronic health records of individual patients. Longitudinal data on individual patients is available and includes inpatient and outpatient data based on visits—ambulatory or inpatient encounters. To obtain data from the TriNetX platform, browser-based real-time analytical features were used (https://open.trinetx.com/trinetx-publication-guidelines/). The query was conducted to obtain records of patients who had the index event from January 2016 to November 2023 (Figure 1). Where necessary, assistance was obtained from the experts and biostatisticians (TriNetX) in building the queries and running the analysis. Most health-care organisation are from the United States—Clinical and Translational Science Awardees and National Cancer Institute–designated cancer centres. Other centres are from Europe, Asia and South America.

2.2 | Query Criteria and Cohort Definitions

Individuals ≥ 16 years of age who were diagnosed with alcohol-associated hepatitis from January 2016 to November 2023 were selected for the study. Patients with alcohol-associated hepatitis were identified using ICD-10-CM code (Supporting Information). We used the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria to define alcohol-associated hepatitis—presence of alcohol use disorder, serum aspartate aminotransferase > 50 U/L but < 400 U/L, serum bilirubin ≥ 3 mg/dL and elevated serum bilirubin for < 8 weeks [1]. However, the ratio of serum aspartate aminotransferase and alanine aminotransferase at a given time cannot be determined. Mean values of serum albumin, bilirubin, creatinine, international normalised ratio (INR) and platelet count at the time of presentation were obtained.

Severe alcohol-associated hepatitis was defined as presence of alcohol-associated hepatitis along with a serum bilirubin of > 5 mg/dL and an INR of 1.5 or more. The laboratory values of serum bilirubin and INR were identified using Logical Observation Identifier Names and Codes. Since we are unable to calculate the model for end-stage liver disease (MELD) score or Maddrey's discriminant function score in individual patients, we used these stringent criteria (serum bilirubin ≥ 5 mg/dL and INR ≥ 1.5) to include only alcohol-associated hepatitis patients with a Maddrey's discriminant function score of > 32 (at least 32.6). This corresponds to a MELD score of at least 18. As per the NIAAA recommendations, patients who underwent liver biopsy with exclusion of other aetiologies of acute hepatitis (as defined below) were categorised as 'definite' alcohol-associated hepatitis and rest of the patients with alcohol-associated hepatitis who did not undergo liver biopsy were 'probable' alcohol-associated hepatitis [1]. We also explored the database to look for patients with had metabolic dysfunction associated steatohepatitis along with alcohol-associated hepatitis using ICD-10 codes.

Patients with other causes of acute hepatitis or acute liver injury—acute viral hepatitis, autoimmune hepatitis, drug-induced liver injury, Wilson, disease, acute hepatic or portal vein thrombosis, biliary obstruction, malignant neoplasms, prothrombotic states, and coumadin use were excluded. Patients with sepsis at the time of inclusion were also excluded.

2.3 | Interventions

Use of medications for the treatment of SAH was identified using Healthcare Common Procedure Coding System and RxNorm (normalised names for all clinical drugs in the United States

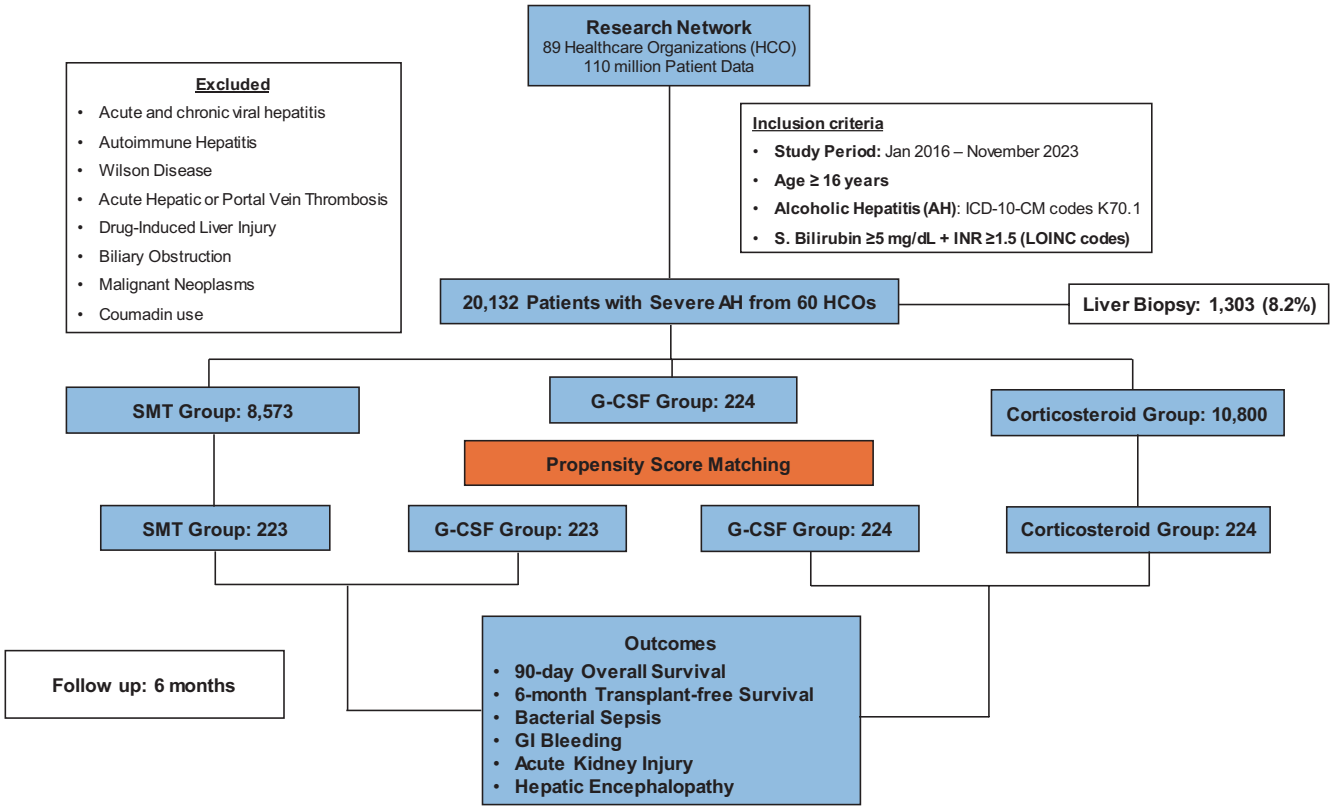

FIGURE 1 | Consort diagram illustrating database search and patient cohort selection strategy.

market). G-CSF included filgrastim, pegfilgrastim and lenograstim. Corticosteroid group received prednisone, prednisolone, methylprednisolone or dexamethasone. Patients who received corticosteroids were excluded from G-CSF cohort and patients who received G-CSF were excluded from the corticosteroid cohort. The mean number (and standard deviation) of G-CSF doses and corticosteroid doses were calculated in the respective cohorts.

2.4 | Follow Up and Clinical Outcomes

Individuals selected for the study were followed up for a median of 6 months following the index events (diagnosis of severe alcohol-associated hepatitis). The index event was defined as the earliest time point after which outcomes are analysed.

Primary outcome: 90-day overall survival in G-CSF group versus corticosteroid group and 90-day overall survival in G-CSF group versus standard medical therapy (SMT = no G-CSF, corticosteroid or NAC) group.

Secondary outcomes: 6-month transplant-free survival in G-CSF group compared with corticosteroid group and 6-month transplant-free survival in G-CSF group compared with SMT group. Other outcomes were the rate of gastrointestinal bleeding, bacterial sepsis, hepatic encephalopathy, and acute kidney injury in patients treated with G-CSF versus those treated with corticosteroids, and G-CSF group versus SMT group.

To ensure adequate follow-up and to minimise loss to follow-up, individuals were assessed for follow-up using inpatient and outpatient visits. Propensity score (1:1) matching was performed to control confounding variables. The analyses included outcomes that occurred in the time window that started 1 day after the first occurrence of the index event and ended 180 days after the first occurrence of the index event. The index event only includes events that occurred up to 20 years ago. Patients whose index event occurred 20 years or more ago are excluded. Since all of them met the criteria for the index event none of the patients in the two cohorts were excluded. The details of index events and outcome criteria are presented in the Supporting Information.

2.5 | Ethical Considerations

'The data reviewed in this retrospective study is a secondary analysis of existing data and does not involve intervention or interaction with human subjects and is de-identified per the de-identification standard defined in Section §164.514 (a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514 (b) (1) of the HIPAA Privacy Rule. This formal determination by a qualified expert refreshed on December 2020' (Publication Guidelines—TriNetX) [14] This study involves human subjects; however, the western institutional review board has provided a waiver to TriNetX since it utilises aggregate counts, and investigators do not have access to protected health information from the participating health-care organisations. Thus, the study is exempt from informed consent. 'To fortify protected health information, TriNetX rounds up the number

of patients to the nearest 10 for analytic purposes'. Specific geographical and institutional data of participating centres are kept anonymous.

2.6 | Statistical Analyses

Mean and standard deviation were calculated for continuous variables, and proportion and percentage were calculated for dichotomous and categorical variables. Age and the comorbidities were also assessed as a proxy for the Charlson comorbidity index since the Charlson comorbidity index of individual patients cannot be calculated in the database (Table 1). For clinical outcomes, risk ratio (RR) and risk difference were calculated, and Kaplan–Meir analysis with survival curve was obtained for median 90-day overall survival and 180-day transplant-free survival. The statistical significance was set at a two-sided $p < 0.05$. All the statistical analyses were performed using the TriNetX platform.

2.7 | Sensitivity Analysis

Propensity score matching was performed. To generate a propensity score, the first step was logistic regression (where the outcome was exposure). Then factors associated with the exposure were determined by evaluating Table 1 (before matching) for variables significantly different between the study and control groups. Propensity score matching was performed to reduce bias in estimating treatment effects and to reduce the likelihood of confounding when analysing non-randomised data. Propensity score matching was based on relevant covariates using greedy nearest neighbour algorithms—matching study and control groups with the highest propensity scores. Characteristics with standard mean difference between cohorts < 0.1 were considered well matched. Characteristics of the cohorts before and after matching are summarised in Table 1.

2.8 | Survival Analysis

Kaplan–Meier analysis was performed on propensity-matched groups. Kaplan–Meier analysis was used to estimate the probability of an outcome at a respective time interval (daily time interval was used in the analysis). To account for the patients who exited the cohort during the analysis period censoring is applied. In this analysis, patients are removed from the analysis (censored) after the last fact in their record. Censoring was applied to account for the patients who exited the cohort during the analysis period to avoid inclusion in the analysis. The output summary includes: Patients in each cohort (count of patients meeting query criteria); Patients with outcome (of the patients in the cohort, count of patients that had the outcome in the time window); Median survival (the number of days when the survival drops below 50% during the time window); and survival probability at end of time window (the % survival at the end of the time window). Log-rank testing was performed to assess statistical differences in time to event for each cohort. Hazard ratios (HR) were calculated using a univariate Cox-proportional model. Cox-proportional hazards model assumes that the chance of each hazard remains similar over time. Analyses were performed at 28, 90 and 180 days for key outcomes.

3 | Results

We identified 82 187 patients with alcohol-associated hepatitis and 20 132 (24.50%) out of them met criteria for severe alcohol-associated hepatitis. Most of the patients were from the United States (~98%, Supporting Information). Eighty percent of patients completed a six-month follow-up. More than half of all patients with severe alcohol-associated hepatitis (53.65%, $N = 10\,800$) were treated with corticosteroids and 224 (1.11%) received G-CSF for at least 5 days, and 8573 (42.58%) did not receive corticosteroids, G-CSF or N-acetyl cysteine. A total of 1198 (5.95%) patients with alcohol-associated hepatitis had definite SAH based on liver biopsy. Patients who received G-CSF were younger (45.5 vs. 48.4 years, $p = 0.002$) White (79.91% vs. 72.40%) and had more comorbidities (Table 1). There was no difference in age or gender between G-CSF and corticosteroid groups; however, the White population received G-CSF more commonly than corticosteroids (80% vs. 73%). Mean values of serum creatinine, bilirubin, and INR at the time of clinical presentation were higher in the G-CSF cohort before propensity matching. Patients with comorbid conditions were more likely to receive G-CSF than corticosteroids. The mean number of G-CSF doses was 8.91 (±3.2).

3.1 | Primary Outcomes

Ninety-day overall survival was significantly higher in the G-CSF cohort compared with SMT (88.31% vs. 62.36%, HR 0.26, 95% CI 0.17–0.41) (Figure 2). More patients in the G-CSF group survived for 90 days compared with the corticosteroid group (88.31% vs. 74.39%, HR 0.38, 95% CI 0.23–0.62) (Figure 2b).

3.2 | Secondary Outcomes

Six-month transplant-free survival was better in the G-CSF group compared with SMT group (83.53% vs. 55.36%, HR 0.30, 95% CI 0.20–0.44), and corticosteroid groups (83.53% vs. 68.15%, HR 0.40, 95% CI 0.26–0.60) (Figure 3a,b). Gastrointestinal bleeding was seen less commonly in patients who received G-CSF compared with SMT (5.02% vs. 14.55%, RR 0.34, 95% CI 0.18–0.66) and corticosteroids (5.02% vs. 13.67%, RR 0.48, 95% CI 0.16–0.62). Bacterial sepsis (21.70% vs. 17.93%, RR 1.21, 95% CI 0.82–1.78), acute kidney injury (43.39% vs. 39.62%, RR 1.09, 95% CI 0.87–1.37), and hepatic encephalopathy (10.85% vs. 15.57%, RR 0.70, 95% CI 0.42–1.15) were observed at similar rates in patients treated with G-CSF and SMT (Table 2). Hepatic encephalopathy was observed more commonly in the corticosteroid group (20.09% vs. 10.85%) compared with G-CSF group (RR 0.55, 95% CI 0.34–0.87). Bacterial sepsis (22.32% vs. 23.66%) and acute kidney injury (44.29% vs. 53.43%) were observed at similar rates in G-CSF and corticosteroid groups (Table 3).

TABLE 1 | Baseline characteristics of patients with severe alcohol-associated hepatitis.

	Before propensity matching			After propensity matching			Before propensity matching			After propensity matching		
Characteristic name	**G-CSF (*N* = 224)**	**SMT (*N* = 8573)**	**SMD**	**G-CSF (*N* = 223)**	**SMT (*N* = 223)**	**SMD**	**G-CSF (*N* = 224)**	**Corticosteroid (*N* = 10 800)**	**SMD**	**G-CSF (*N* = 224)**	**Corticosteroid (*N* = 224)**	**SMD**
Demographics												
Mean age +/−SD (years)	47.22 ± 11.33	48.4 ± 11.4	0.12	47.22 ± 11.33	47.34 ± 10.8	0.06	47.22 ± 11.33	46.71 ± 11.6	0.05	47.22 ± 11.33	46.8 ± 11.5	0.01
Female	86 (36.44%)	3428 (37.70%)	0.03	86 (36.44%)	80 (36.20)	< 0.01	86 (36.44%)	4888 (37.46%)	0.05	86 (36.44%)	88 (37.29%)	0.01
White	180 (76.27%)	(70.34%)	0.19	174 (78.73%)	174 (78.73%)	< 0.01	180 (76.27%)	9265 (71.01%)	0.29	180 (76.27%)	191 (80.93%)	0.03
Hispanic or Latino	18 (7.62%)	1017 (11.19%)	0.10	18 (7.62%)	22 (9.96%)	0.07	18 (7.62%)	1344 (10.30%)	0.10	18 (7.62%)	20 (8.48%)	0.10
African American	10 (4.23%)	768 (8.45%)	0.16	10 (4.23%)	14 (6.33%)	0.08	10 (4.23%)	1071 (8.21%)	0.15	10 (4.23%)	10 (4.24%)	< 0.01
Mean lab values (blood/serum)												
Creatinine ± SD	1.73 ± 1.54	1.10 ± 1.0	0.54	1.74 ± 1.45	1.68 ± 1.09	0.06	1.73 ± 1.54	1.35 ± 1.23	0.25	1.74 ± 1.56	1.53 ± 1.15	0.08
Albumin ± SD	3.19 ± 0.72	2.93 ± 0.77	0.34	3.20 ± 0.74	2.97 ± 0.71	0.10	3.12 ± 0.72	2.82 ± 0.65	0.72	3.12 ± 0.72	2.99 ± 0.68	0.07
Total Bilirubin ± SD	7.16 ± 3.8	8.14 ± 4.28	0.17	7.16 ± 3.94	7.99±	0.09	7.16 ± 3.8	9.60 ± 3.94	0.39	6.94 ± 4.56	7.85 ± 5.44	0.09
INR ± SD	1.89 ± 0.68	1.73 ± 0.41	0.25	1.89 ± 0.54	1.84 ± 0.43	0.05	1.89 ± 0.68	2.11 ± 1.15	0.41	1.92 ± 0.73	2.07 ± 0.90	0.07
Platelet count ± SD	142 ± 111	138 ± 97	0.18	143 ± 111	141 ± 106	< 0.01	142 ± 111	129 ± 88	0.10	143 ± 112	135 ± 96.9	0.07
Comorbidities												
Cirrhosis of liver	205 (86.86%)	4225 (46.47%)	1.11	203 (91.03%)	204 (91.48%)	0.01	205 (86.86%)	150 (63.56%)	0.56	205 (86.86%)	203 (86.02%)	< 0.01
Chronic kidney disease	112 (47.46%)	755 (8.30%)	1.28	112 (50.22%)	115 (51.57%)	0.02	112 (47.46%)	1244 (9.53%)	1.03	112 (47.46%)	120 (50.85%)	< 0.01
Overweight and obesity	76 (33.93%)	1359 (14.95%)	0.56	75 (36.6%)	79 (35.43%)	0.04	76 (33.93%)	2571 (19.70%)	0.35	76 (32.20%)	78 (33.05%)	0.03
Diabetes mellitus	71 (30.08%)	1149 (12.64%)	0.52	71 (31.84%)	71 (31.84%)	< 0.01	71 (30.08%)	1708 (13.09%)	0.48	71 (30.08%)	66 (27.97%)	0.06
Ischemic heart diseases	48 (20.34%)	892 (9.81%)	0.46	48 (21.52%)	45 (20.18%)	0.04	48 (20.34%)	1312 (10.05%)	0.33	48 (20.34%)	55 (23.31%)	0.03
Chronic respiratory diseases	38 (16.10%)	1202 (13.22%)	0.19	38 (17.04%)	36 (16.14%)	0.06	38 (16.10%)	2201 (16.87%)	0.02	38 (16.10%)	39 (16.53%)	0.01
Heart failure	34 (14.41%)	693 (17.49%)	0.30	34 (15.25%)	35 (15.70%)	0.01	34 (14.41%)	1069 (8.19%)	0.23	34 (14.41%)	34 (14.41%)	< 0.01

Abbreviations: G-CSF, granulocyte colony-stimulating factor; *N*, number of patients in each cohort; SD, standard deviation; SMT, standard medical treatment; SMD, standard mean difference.

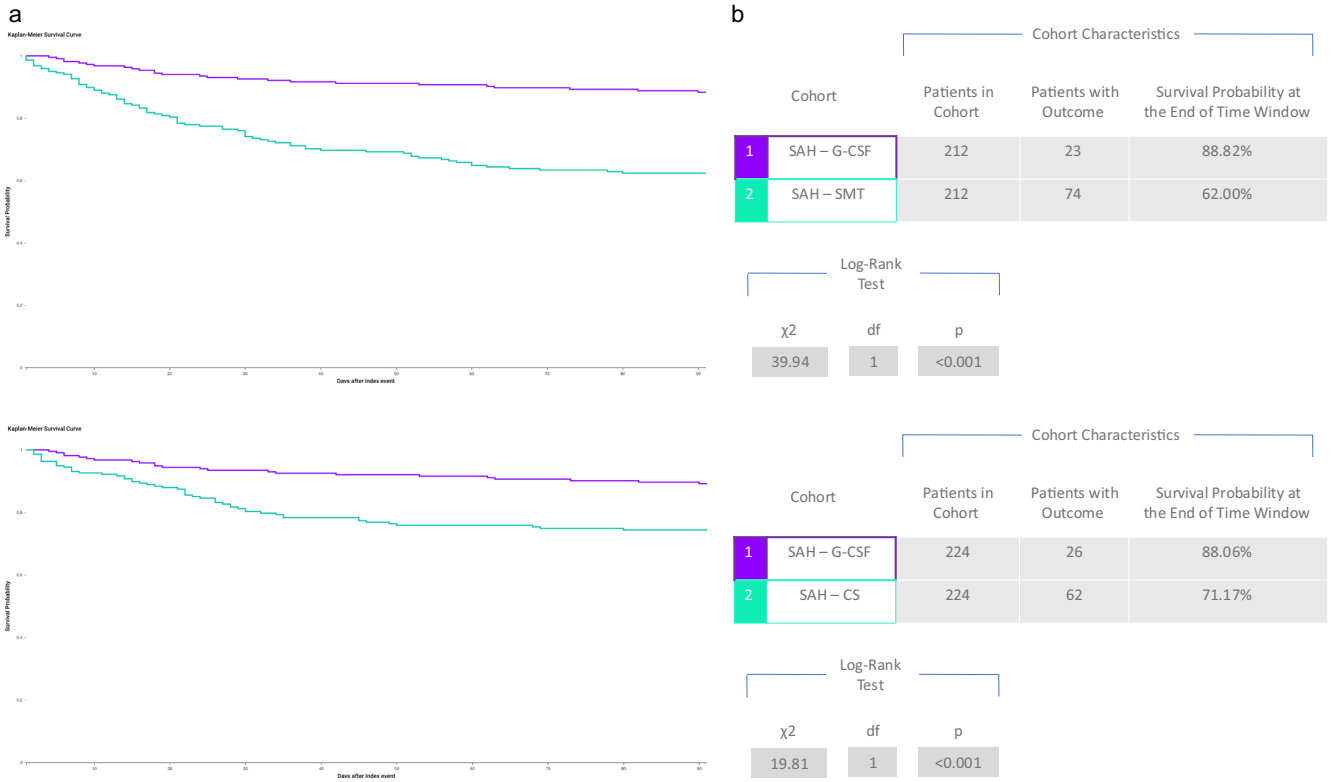

FIGURE 2 | (a) Kaplan–Meier graph for 90-day overall survival G-CSF versus standard medical therapy in patients with severe alcohol-associated hepatitis. (b) Kaplan–Meier graph for 90-day overall survival G-CSF versus Corticosteroid. SAH_G-CSF severe alcohol-associated hepatitis treated with granulocyte colony-stimulating factor (G-CSF), SAH_SMT, severe alcohol-associated hepatitis treated with standard medical therapy, SAH_CS, severe alcohol-associated hepatitis treated with corticosteroid, df, degree of freedom.

4 | Discussion

Current guidelines recommend treatment of SAH with corticosteroids in the absence of contraindications [1, 15]. However, overall short-term survival is poor in patients who are excluded from corticosteroid therapy due to contraindications or failure to respond to such therapy. One of the alternatives to corticosteroids studied in the treatment of SAH is G-CSF. Multiple prospective studies from India have shown improvement in 1- to 3-month survival [10–12, 16]. Nonetheless, these studies are small scale with cumulative number of patients treated with G-CSF in these trials is about 100. Engelmann et al., in a multicentre randomised trial of G-CSF in acute-on-chronic liver failure (GRAFT study), did not find a survival advantage of G-CSF over standard therapy alone [13]. Alcohol-associated hepatitis comprised about half of the precipitating events in each cohort ($N = 55$ in G-CSF group). These results do not support the use of G-CSF in SAH.

To the best of our knowledge, we provide the largest data, albeit retrospective, on the use of G-CSF to treat SAH. Our results indicate that corticosteroids remain the primary treatment of choice for severe alcohol-associated hepatitis, and the use of G-CSF remains limited. The limited use of G-CSF reflects lack of clear data. In an age-, gender- and comorbidity-matched cohort of patients, we observed a significant improvement in 90-day overall survival of SAH patients treated G-CSF compared with standard medical therapy (HR = 0.26) and corticosteroids (HR = 0.38). Our findings are in line with most of the previously published studies which have demonstrated a 90-day survival advantage of G-CSF compared with SMT [10–12]. However, the positive result in Asian studies is limited by small sample size. While the GRAFT study is the largest multicentre randomised trial from the West, it has several limitations [13]. The authors primarily studied acute-on-chronic liver failure and do not provide subgroup analysis of patients with each precipitating factor. Only 33% of patients completed all the planned doses of G-CSF in the intervention group, and we do not know how many of them had alcohol-associated hepatitis. Many patients had more than one precipitating event. Furthermore, about half of the patients had active infection at the time randomisation and bacterial infection was the precipitating event in about 40% of the G-CSF arm. Thus, we cannot extrapolate the results of this study to the SAH population.

There is no published study comparing G-CSF and corticosteroid therapy. Thus, despite the retrospective study design, we present novel findings of non-inferior overall survival in G-CSF treated patients compared with corticosteroids. Furthermore, we found a significant improvement in 6-month transplant-free survival among patients who were treated with G-CSF compared with standard medical therapy (HR = 0.30) or corticosteroid (HR = 0.36). The data on transplant-free survival in patients treated with G-CSF is limited.

Previous studies evaluating the role of G-CSF in SAH are almost exclusively from Asia (India) and there is lack of robust data in White population. A meta-analysis by Marot et al.

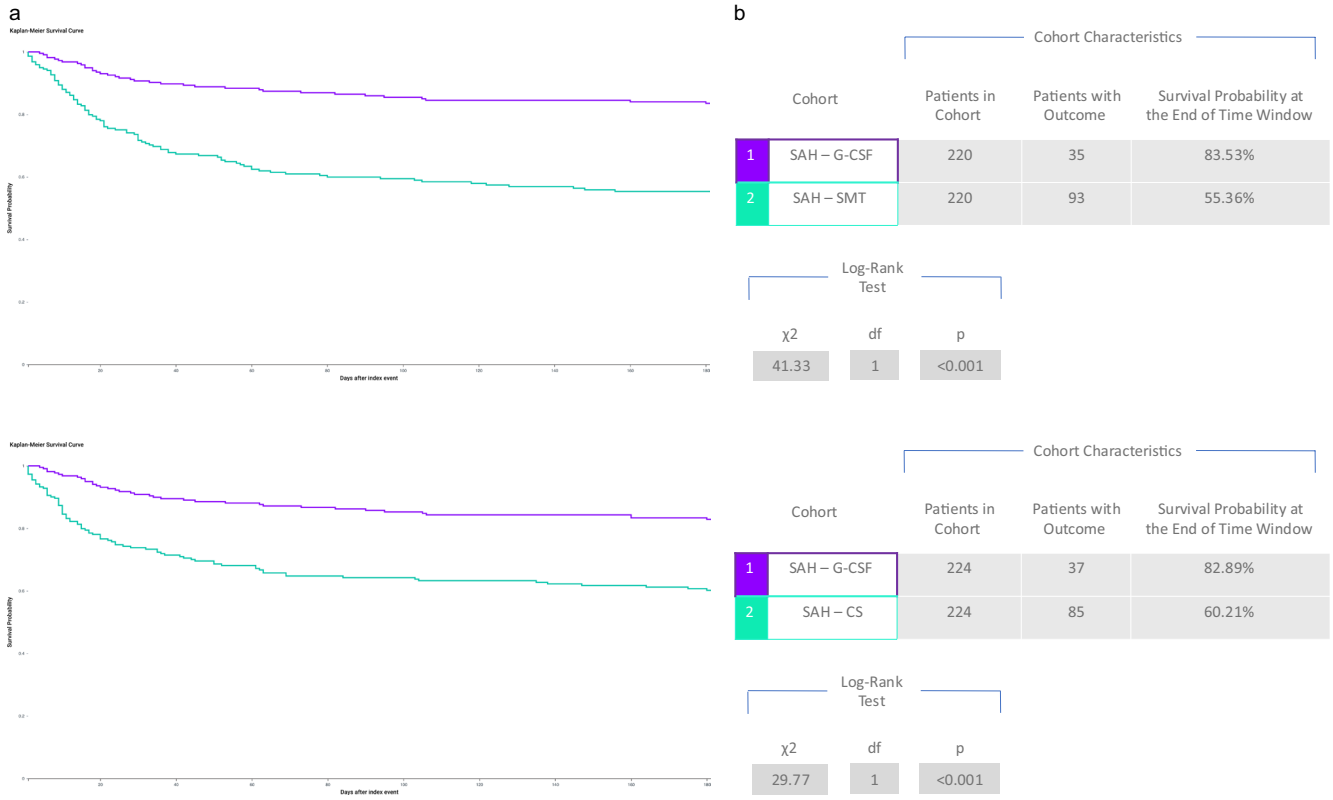

FIGURE 3 | (a) Kaplan–Meier graph for 6-month transplant-free survival G-CSF versus SMT. (b) Kaplan–Meier graph for 6-month transplant-free survival G-CSF versus Corticosteroid. SAH_G-CSF severe alcohol-associated hepatitis treated with granulocyte colony-stimulating factor (G-CSF), SAH_SMT, severe alcohol-associated hepatitis treated with standard medical therapy, SAH_CS, severe alcohol-associated hepatitis treated with corticosteroid, df, degree of freedom.

TABLE 2 | Secondary outcomes in severe alcohol-associated hepatitis patients treated with G-CSF and standard medical therapy after propensity score matching.

	Number (%) with outcome				
Clinical outcomes	**G-CSF ($N=220$)**	**SMT ($N=220$)**	**Risk ratio**	**95% CI**	***p***
6-month transplant-free survival	185 (83.53%)	127 (55.36%)	HR = 0.30	0.20–0.44	< 0.001
GI bleeding	11 (5.02%)	32 (14.55%)	0.34	0.18–0.66	< 0.001
Acute kidney injury	97 (43.39%)	89 (39.62%)	1.09	0.87–1.37	0.05
Bacterial sepsis	46 (20.53%)	38 (17.93%)	1.21	0.82–1.78	0.42
Hepatic encephalopathy	24 (10.85%)	32 (15.57%)	0.70	0.42–1.15	0.67

Abbreviations: CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; HR, hazard ratio; SMT, standard medical therapy.

showed conflicting survival outcomes between the Asian and European countries [17]. In the meta-analysis, the results from Asian studies showed that G-CSF was associated with a better survival while the European studies found no difference in survival. We performed a propensity-matched analysis of patients from all geographic areas in the United States. About 80% ($N=180$) of patients treated with G-CSF were Whites, which is the largest representation of White population treated with G-CSF for this indication. The largest published data in White population is by Engleman et al.; however, the study does not provide direct evidence to refute use of G-CSF in SAH per se [13].

We found a lower rate of gastrointestinal bleeding in patients treated with G-CSF; however, bacterial sepsis, hepatic encephalopathy, acute kidney injury and hepatorenal syndrome were seen at similar rates across both the groups [G-CSF versus SMT]. This is an interesting finding and contrasts with most of the Asian studies which have shown lower rate of sepsis in patients who received G-CSF [11, 12, 16]. In contrast, the GRAFT study did not show any difference in bacterial infections between G-CSF and SMT arms; however, more than half of the patients in each cohort had infections at baseline [13]. In a randomised controlled trial by Tayek et al., patients with SAH who received standard of care treatment versus pegfilgrastim also showed

TABLE 3 | Secondary outcomes in severe alcohol-associated hepatitis patients treated with G-CSF and corticosteroids after propensity score matching.

Clinical outcomes	Number (%) with outcome		Risk ratio	95% CI	*p*
	G-CSF (*N* = 224)	Corticosteroid (*N* = 224)			
6-month transplant-free survival	187 (82.89%)	139 (60.21%)	HR = 0.40	0.26–0.60	< 0.001
GI bleeding	11 (5.02%)	32 (13.67%)	0.48	0.16–0.62	< 0.001
Acute kidney injury	97 (43.39%)	4099 (31.03%)	1.35	1.16–1.57	0.004
Bacterial sepsis	46 (20.53%)	49 (21.43%)	0.84	0.55–1.28	0.38
Hepatic encephalopathy	24 (10.85%)	22 (10.28%)	0.61	0.23–1.18	0.54

Abbreviations: CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; HR, hazard ratio.

similar incidences of adverse outcomes (sepsis, hepatic encephalopathy, acute kidney injury and hepatorenal syndrome) among the two groups. However, the study did not find an improvement in survival at 90 days in the G-CSF group [18]. Another noteworthy finding in our study was that patients treated with G-CSF had more comorbidities than reported by Asian studies [11, 16]. However, it is important to note that patients in our study were older, and the Western population (specially, the US population) is known to have more comorbidities. Furthermore, compared with SMT and corticosteroid groups the G-CSF group had more comorbidities. This probably represents selection of sicker patients to G-CSF treatment. By performing propensity matching for comorbidities, we reduced the risk of this potential selection bias.

4.1 | Strengths and Limitations

With the inclusion of 89 health-care organisations from various geographic regions within the US with access to over 100 million patient health records, our results are generalisable and applicable to the US population. Despite being retrospective, the cohort study design tends to reduce the risk of selection bias. The study also provides an unbiased comparison of overall survival in SAH patients. Additionally, propensity score matching reduces the probability of confounding and may provide a useful approximation of the likely effect of G-CSF and corticosteroid treatment in patients with SAH.

Our study has some notable limitations. The retrospective study design is associated with risk of bias. While the database utilises electronic health records for research purposes, detailed clinical data of individual patients is unavailable due to lack of access to protected health information. The diagnosis of SAH is based on ICD 10 code and laboratory values (serum bilirubin and INR). Response to corticosteroid therapy using Lille score could not be performed in individual patients. Our clinical outcomes are overall and transplant-free survival. The database does not provide information on the dose of G-CSF; however, patients received a mean of about seven doses of G-CSF. The database does not provide information about return to alcohol use and alcohol relapse rate, and this can affect the 90-day and 6-month survival endpoints. TriNetX performs extensive data quality assessment to reduce the risk associated with data collection. However, as with any other database, conversion of patient's clinical data into codes can result in errors. Unadjusted confounding may exist despite matching if unmeasured factors influenced treatment selection. The database does not provide information on the cause of death. Potential loss of patients can occur due to transfer from one health-care organisation to another; however, over 80% of patients completed 6 months of follow-up.

In summary, our results demonstrate that G-CSF is non-inferior to corticosteroids in the treatment of severe alcohol-associated hepatitis. However, its use remains controversial and has not yet received widespread endorsement from the global hepatology community. Published data from the West is limited and shade doubts on the benefit of G-CSF for this indication. Nonetheless, our study stands as one of the largest multicentric studies till date and shows that sun is not down yet for the role of G-CSF in severe alcohol-associated hepatitis. Multicenter prospective head-to-head studies comparing corticosteroids and G-CSF can underpin the role of G-CSF as one of the first-line treatment options for severe alcohol-associated hepatitis—hopefully providing the window of opportunity for these patients to recover and preclude liver transplantation.

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Ethics Statement

This has been provided in Section 2.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.