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Pentoxifylline use in alcohol-associated hepatitis with acute kidney injury does not improve survival: a global study

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ABSTRACT

Background Severe alcohol-associated hepatitis (sAH) is a life-threatening condition with high mortality, where corticosteroid use is the only treatment that has shown short-term benefits. Pentoxifylline, an anti-tumour necrosis factor-alpha agent, has been proposed for its potential to improve outcomes, especially in patients with acute kidney injury (AKI). We aimed to evaluate the impact of pentoxifylline on mortality in patients with sAH and AKI in a well-characterised global cohort.

Methods We conducted a retrospective, registry-based study including patients meeting the National Institute on Alcohol Abuse and Alcoholism clinical criteria for sAH and AKI. Mortality was the primary endpoint, with liver transplantation as a competing risk. Statistical analysis included Cox regression and Kaplan-Meier survival estimates.

Results We included 525 patients from 20 centres across eight countries. The median age was 48 years, with 26.1% females, and 76.9% had a history of cirrhosis. Multivariable Cox regression models showed that pentoxifylline use was not associated with survival (HR 1.20, 95% CI 0.85 to 1.69, p=0.291). Factors associated with mortality included age (HR 1.23, 95% CI 1.10 to 1.36, p<0.001), Model for End-Stage Liver Disease score at admission (HR 1.06, 95% CI 1.04 to 1.08, p<0.001) and renal replacement therapy use (HR 1.39, 95% CI 1.05 to 1.84, p=0.019). The main causes of death were multiple organ failure (42%), infections (10%), oesophageal varices bleeding (7%) and renal failure (6%).

Conclusion Pentoxifylline showed no significant benefit on mortality in patients with sAH and AKI. Further studies are needed to refine treatment strategies for this high-risk group.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe alcohol-associated hepatitis (sAH) is associated with high mortality, and the efficacy of pentoxifylline, an anti-inflammatory agent, remains uncertain as a treatment for patients with sAH and acute kidney injury (AKI).

WHAT THIS STUDY ADDS

⇒ This study, which analysed a large cohort of patients with sAH and AKI, found no evidence of a survival benefit associated with pentoxifylline use at either 30 or 90 days, raising questions about its clinical utility in this population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The lack of benefit of pentoxifylline in sAH and AKI underscores the need for further research on more effective treatments, including novel agents or combination therapies, to improve patient outcomes.

INTRODUCTION

Severe alcohol-associated hepatitis (sAH), an acute manifestation of alcohol-associated liver disease, is a life-threatening condition characterised by rapid onset of jaundice and decompensated liver function.[1 2] Patients with sAH frequently develop complications such as bacterial infections, acute-on-chronic liver failure and multiorgan failure, contributing to a 28-day mortality rate of approximately 30% and a 1-year mortality rate approaching 50%.[3] Despite extensive research on various therapies, the management of sAH remains focused on alcohol abstinence, nutritional counselling and general supportive measures. Additionally, in patients with Model for End-Stage Liver Disease (MELD) scores between 21 and 39, corticosteroid use has shown a

reduction in 1-month mortality. However, it offers no survival benefits beyond that timeframe.[4 5]

Pentoxifylline, an oral anti-tumour necrosis factor-alpha (anti-TNF-α) agent, has been proposed as a treatment for sAH to counteract the elevation of serum TNF-α levels associated with this disease[6] that could increase the production of intracellular oxygen-free radicals and lead to cellular apoptosis.[7] The evidence regarding the use of pentoxifylline in the treatment of sAH has been heterogeneous; some studies would describe an increase in early survival, while others would deny this alleged benefit.[5 6 8 9] Despite the conflicting evidence, pentoxifylline is a therapy frequently used in certain regions of the world, with usage rates approaching 15% in the Americas, while in Central America and Africa, its use reaches more than 40% among patients with sAH.[10]

The use of pentoxifylline in acute kidney injury (AKI) has been studied in multiple settings. Theoretically, pentoxifylline can suppress the production of inflammatory response factors and potentially prevent AKI. This therapy has shown benefits, including preventing AKI in rat models; and in humans, it has demonstrated a preventive role in the development of AKI before cardiac surgery.[11–14] Additionally, pentoxifylline has been shown to mitigate renal damage in patients with diabetes mellitus[15] and reduce proteinuria or decline in glomerular filtration rate in early chronic kidney disease.[16] Pentoxifylline has been proposed as a potential therapeutic option for sAH, especially for patients with AKI. However, to date, there are no studies specifically investigating this therapy in this patient population. Therefore, the evidence remains insufficient to make clinical decisions regarding the use of this drug in patients with sAH and AKI. It is essential to gather more data on the role of pentoxifylline in this context. This study aims to determine whether the use of pentoxifylline benefits mortality in patients with sAH.

MATERIALS AND METHODS

Study design and participants

The study was conducted using a multicentre retrospective cohort of patients admitted with sAH, included a total of 20 centres from eight countries on three continents (Global AlcHep – a BigData Network). The detailed design of the multicentre retrospective cohort has been previously described in detail.[4] We aimed to evaluate the impact of pentoxifylline on mortality in patients with sAH and AKI. Patients were selected based on clinical criteria established by the National Institute on Alcohol Abuse and Alcoholism[17] and presented with AKI. Patients in the study met the following criteria: a history of alcohol intake exceeding 60 g/day for men and 40 g/day for women, aspartate aminotransferase (AST) levels below 400 IU/L with an AST/alanine aminotransferase (ALT) ratio >1.5, serum γ-glutamyl transpeptidase >80 mg/dL, total bilirubin levels >3.0 mg/dL and evidence of coagulopathy (prolonged prothrombin time or elevated international normalised ratio (INR)).

AKI was defined according to the Acute Kidney Injury Network as an increase in serum creatinine levels ≥50% or 0.3 mg/dL.[18] In an exploratory analysis, only patients with more severe AKI, defined as creatinine ≥1.5 mg/dL, were also evaluated. Cirrhosis was diagnosed based on the clinical history and imaging techniques such as ultrasound, transient elastography, computed tomography or magnetic resonance imaging.

Exclusion criteria comprised patients younger than 18 years, pregnant individuals, those with AST or ALT levels over 400 IU/L, patients abstinent from alcohol for more than 60 days before presentation and cases of drug-induced liver injury, ischaemic hepatitis, biliary obstruction, viral hepatitis, autoimmune hepatitis or Wilson's disease. Further exclusions included hepatocellular carcinoma outside Milan criteria, malignancies with life expectancy under 6 months and severe extrahepatic conditions predicting survival below 6 months.

Data collection

A retrospective analysis was performed by reviewing the medical records of hospitalised patients diagnosed with sAH according to the specified criteria, spanning from January 2009 to January 2019. Laboratory results from the time of admission were recorded. However, data on the quantity of alcohol consumption, the achievement of abstinence following sAH episodes or initiation of therapy for alcohol use disorder (AUD) were unavailable. All collected data were recorded in a confidential electronic case report form, which was managed by the main researchers of the study. Access to patient data was restricted to the research team, and a waiver of informed consent was granted by each participating centre. The study obtained a consent waiver from each local Institutional Review Board.

Statistical analysis

The primary endpoint was time to death. As a secondary endpoint, we conducted a competing risk analysis, accounting for liver transplantation as a competing event. The time to death since admission was calculated as the death date minus admission date+1 day. For competing risks analysis, the time to liver transplantation was calculated as the earlier of the time of transplantation or death minus admission date+1 day.

First, the single event of death was explored, stratified by the use of pentoxifylline. Associations were explored using Cox proportional hazards regression, and the overall number and rate of mortality at selected time points were tabulated. Kaplan-Meier estimates of survival rates were estimated by pentoxifylline use, including 95% CIs. Multivariable Cox regression model selection was conducted using stepwise selection admitting factors with a p value <0.05. Competing risks regression was conducted to examine the event-specific cumulative incidence functions, as well as the subdistribution HRs (sHRs) for death. The Pepe-Mori test was used to compare whether cumulative incidence functions differ across pentoxifylline

Table 1 Baseline characteristics of patients according to the use of pentoxifylline

	Global (n=525)	Pentoxifylline group (n=47)	Control group (n=478)	P value
Age (years), median (IQR)	48 (39–56)	47 (38–54)	48 (39–56)	0.436
Sex (female), n (%)	137 (26.1)	8 (17)	129 (27)	0.430
MELD, median (IQR)	35 (30–40)	35 (33–40)	35 (29–40)	0.174
History of cirrhosis, n (%)	404 (76.9)	33 (70.2)	371 (77.6)	0.225
Use of corticosteroids, n (%)	203 (38.9)	14 (29.7)	189 (39.5)	0.899
Infections during hospitalisation, n (%)*	156 (59.1)	6 (37.5)	150 (60.5)	0.038
Laboratory testing at admission				
Total bilirubin (mg/dL)	21.2±12.3	25.5±10.7	20.8±12.4	0.002
International normalised ratio	2.34±1.43	2.17±0.74	2.36±1.49	0.642
Sodium (mEq/L)	130±7.7	131±8.44	129±7.59	0.129
Albumin (g/dL)	2.5±0.7	2.6±0.7	2.5±0.7	0.419
Liver transplant rate, n (%)	35 (6.6)	2 (4.2)	33 (6.9)	0.038

*Missing data were 47.24%, so the analysis was performed with only 248 patients who had records available.
IQR, Interquartile Range; MELD, Model for End-Stage Liver Disease.

use groups for each specific endpoint of death and transplantation.

RESULTS

We included 525 patients with sAH from 20 centres across eight countries spanning three continents. The median age was 48 years (IQR: 39–56). Females comprised 26.1% (n=137) of the cohort. The median MELD score was 35 (IQR: 30–40), and 76.9% (n=404) had a history of cirrhosis. Corticosteroid use was reported in 38.9% (n=203), and infections during hospitalisation occurred in 59.1% (n=156) (table 1).

The pentoxifylline group (n=47) and control group (n=478) had similar median ages (47 (IQR: 38–54) vs 48 (IQR: 39–56), p=0.436) and female representation (17% vs 27%, p=0.430). The MELD scores were comparable (35 (IQR: 33–40) vs 35 (IQR: 29–40), p=0.174). The frequency of a history of cirrhosis did not significantly differ between the pentoxifylline group and the control group (70.2% vs 77.6%, p=0.225). Corticosteroid use was also similar (29.7% vs 39.5%, p=0.899). Infections during hospitalisation were significantly less frequent in the pentoxifylline group (37.5% vs 60.5%, p=0.038). However, there were significant missing data (47.24% of the patients in the cohort had no record of infections). Regarding laboratory parameters, the pentoxifylline group showed higher total bilirubin levels (25.5±10.7 vs 20.8±12.4 mg/dL, p=0.002). No significant differences were observed in INR (2.17±0.74 vs 2.36±1.49, p=0.642), sodium (131±8.44 vs 129±7.59 mEq/L, p=0.129) or albumin (2.6±0.7 vs 2.5±0.7 g/dL, p=0.419). The liver transplant rate was lower in the pentoxifylline group (4.2%, n=2 vs 6.9%, n=33, p=0.038) (table 1).

In survival analysis considering death as the only outcome of interest, Kaplan-Meier estimates of survival in the pentoxifylline use group at 30, 90 and 180 days were 63.8% (95% CI 48.3% to 75.7%), 46.2% (95% CI 31.5% to 59.7%) and 39.6% (95% CI 25.6% to 53.2%), respectively, whereas they were 63.7% (95% CI 59.1% to 67.9%), 49.8% (95% CI 45.1% to 54.3%) and 45.6% (95% CI 40.9% to 50.2%) in the control group (figure 1).

Multivariable Cox regression models showed that pentoxifylline use was similar and not statistically significantly associated with an increased risk of death (adjusted HR 1.20, 95% CI 0.85 to 1.69, p=0.291). In multivariable Cox regression models, risk factors such as age (HR 1.23, 95% CI 1.10 to 1.36, p<0.001), MELD score at admission (HR 1.06, 95% CI 1.04 to 1.08, p<0.001) and renal replacement therapy use (HR 1.39, 95% CI 1.05 to 1.84, p=0.019) were statistically significantly associated with mortality (table 2). In a separate Cox model considering a possible interaction between MELD score at admission and pentoxifylline use, no interaction effect was observed (likelihood ratio p=0.583) (table 3).

In the univariable competing risks regression, the sHR was not statistically significant for pentoxifylline use (sHR 1.24, 95% CI 0.91 to 1.69, p=0.181) and was similar to the Cox regression result. Similarly, the Pepe-Mori test did not indicate differences in the cumulative incidence function of mortality (p=0.305). The main causes of mortality in both groups were multiple organ failure (42%), infections (10%), oesophageal varices bleeding (7%) and renal failure (6%) (p=0.239).

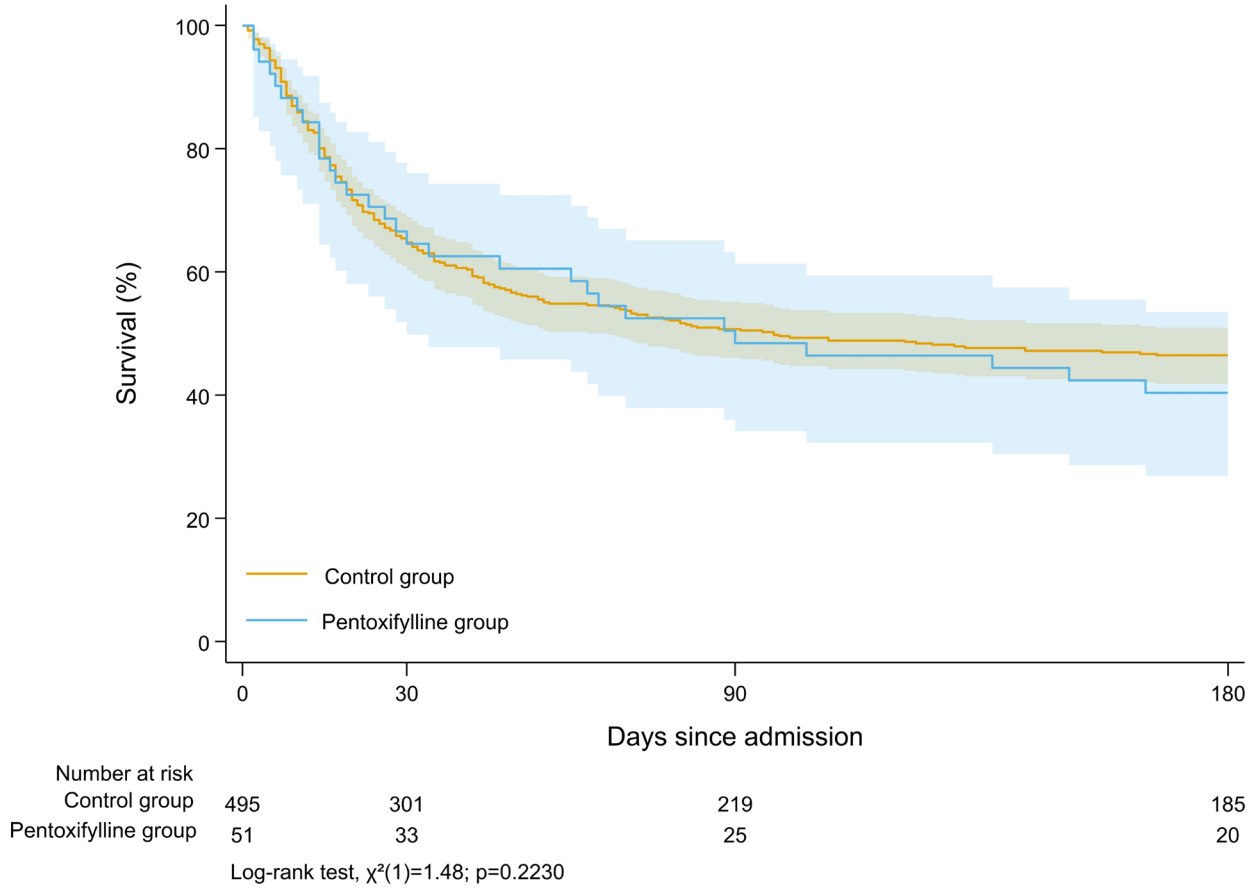

Figure 1 Kaplan-Meier curve of survival by pentoxifylline use.

In the exploratory analysis including only patients with creatinine >1.5 mg/dL, the control group demonstrated similar mortality trends across time points regardless of pentoxifylline use. The Kaplan-Meier survival estimates for the pentoxifylline group at 30, 90 and 180 days were 60.4% (95% CI 44.2% to 73.2%), 43.5% (95% CI 28.4% to 57.6%) and 38.6% (95% CI 24.2% to 52.9%), respectively, in the survival analysis. Meanwhile, the control group showed survival estimates of 62.2% (95% CI 57.1% to 66.8%), 47.3% (95% CI 42.2% to 52.2%) and 43.4% (95% CI 38.3% to 48.4%) at the corresponding time points (figure 2).

In the univariable Cox regression models, pentoxifylline use was not significantly associated with time to

Table 2 Univariable and multivariable Cox regression models for time to death

	Univariable analysis			Multivariable analysis		
Variables	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Pentoxifylline use	1.19	0.86 to 1.64	0.297	1.20	0.85 to 1.69	0.291
Gender	0.73	0.56 to 0.95	0.018	–		
Age	1.10	1.00 to 1.21	0.049	1.23	1.10 to 1.36	<0.001
Cirrhosis	1.02	0.75 to 1.38	0.907	–		
MELD score at admission	1.05	1.04 to 1.07	<0.001	1.06	1.04 to 1.08	<0.001
Use of corticosteroids	1.11	0.89 to 1.38	0.348	–		
Infection at admission	1.48	1.07 to 2.04	0.017	–		
Albumin at admission	0.79	0.68 to 0.93	0.005	–		
Creatinine at admission	1.09	1.03 to 1.15	0.004	–		
Total bilirubin at admission	1.01	1.00 to 1.02	0.012	–		
Renal replacement therapy	1.74	1.36 to 2.24	<0.001	1.39	1.05 to 1.84	0.019

HR, Hazard Ratio; MELD, Model for End-Stage Liver Disease.

Table 3 Stratified and unstratified analyses of pentoxifylline use and admission MELD score

Variables	HR	95% CI	P value
Unstratified (null) model			
Pentoxifylline use	1.13	0.82 to 1.57	–
MELD score at admission (per 1 point increase)	1.68	1.44 to 1.97	–
Stratified (interaction) model			
Pentoxifylline use	0.58	0.05 to 6.18	
MELD score at admission (per 1 point increase)	1.05	1.04 to 1.07	
Pentoxifylline by MELD score interaction	1.02	0.96 to 1.09	
Likelihood ratio test	–	–	0.583

Cox proportional hazards regression model was used containing the factors listed under the stratified or unstratified models, respectively. The likelihood ratio test compares the interaction (stratified) model against the null hypothesis model of no interaction.
HR, Hazard Ratio; MELD, Model for End-Stage Liver Disease.

death (HR 1.15, 95% CI 0.81 to 1.63, p=0.433). Significant predictors of mortality included age (HR 1.12, 95% CI 1.01 to 1.23, p=0.025), gender (HR 0.73, 95% CI 0.54 to 0.97, p=0.028), MELD score (HR 1.05, 95% CI 1.03 to 1.07, p<0.001), use of renal replacement therapy (HR 1.65, 95% CI 1.27 to 2.14, p<0.001), albumin at admission (HR 0.81, 95% CI 0.68 to 0.96, p=0.013) and creatinine at admission (HR 1.08, 95% CI 1.01 to 1.14, p=0.021). Independent predictors of mortality included age (HR 1.25 per decade, 95% CI 1.12 to 1.40, p<0.001), MELD score (HR 1.06, 95% CI 1.04 to 1.08, p<0.001) and renal replacement therapy use (HR 1.41, 95% CI 1.06 to 1.87, p=0.017) (table 4).

DISCUSSION

sAH is a life-threatening condition that is associated with high mortality, especially in the presence of AKI, which complicates the management of affected patients.[3] The potential role of pentoxifylline, an anti-TNF-α agent, in reducing mortality in patients with sAH has been explored in multiple studies. However, the results have been inconclusive, with some studies suggesting a benefit in early survival, while others have found no improvement in outcomes.[5 6 8 9] Our study, a large retrospective analysis, aimed to evaluate the impact of pentoxifylline on mortality in patients with sAH who develop AKI, particularly due to the protective effect that pentoxifylline has been shown to have in AKI in other settings. The results of our study did not demonstrate any significant benefit in terms of survival associated with pentoxifylline use.

The relationship between AKI and sAH has been extensively studied. AKI is a frequent and early complication in patients with sAH, and those who develop AKI experience a significant impact on their short-term prognosis.[19] Interestingly, it has been shown that the degree of systemic inflammatory response and liver failure are the main factors predicting the development of AKI. Therefore, managing infections reduces the risk of AKI and, consequently, mortality.[20 21] Given the effect demonstrated by pentoxifylline, due to its role in suppressing the production of inflammatory response factors in rat models and in patients, particularly in the context of acute tubular necrosis,[11–14] its potential utility in sAH seemed to be an interesting therapy. This is especially true when considering the significant inflammatory factors associated with this condition, as well as the frequent and detrimental occurrence of AKI in sAH.[22] Despite this, it is likely that the effect of pentoxifylline in sAH does not have a significant impact on the inflammatory factors and the pathways that lead to renal failure and mortality in such a severe condition.

Despite this theoretical benefit, our findings align with several previous studies that failed to demonstrate a survival benefit from pentoxifylline in patients with sAH.[5 8 9] Our data confirm that even in those with AKI, there was no survival benefit. The absence of a survival benefit in our cohort supports the findings of these studies and suggests that pentoxifylline, although commonly used in certain regions of the world, may not be as effective and should not be used given the lack of demonstrated benefit. Additionally, we performed an exploratory analysis in a subset of patients with more severe AKI, defined as serum creatinine greater than 1.5 mg/dL, to determine if pentoxifylline had a more pronounced effect in this particularly vulnerable subgroup. Again, no significant difference in mortality was observed between the pentoxifylline and control groups, reinforcing our primary finding that pentoxifylline does not improve survival in patients with severe sAH complicated by AKI.

We identified several independent predictors of mortality, including age, MELD score at admission, infections and the need for dialysis. These traditional risk factors have been well established in the literature as strong predictors of poor outcomes in patients with sAH.[2] Notably, the lack of association between pentoxifylline use and mortality, even after adjusting for these risk factors, underscores the relative importance of disease severity and the need for appropriate supportive care in determining patient outcomes. In contrast, factors such as age, infections and dialysis requirements were consistently associated with a higher risk of death, highlighting the importance of early intervention and comprehensive

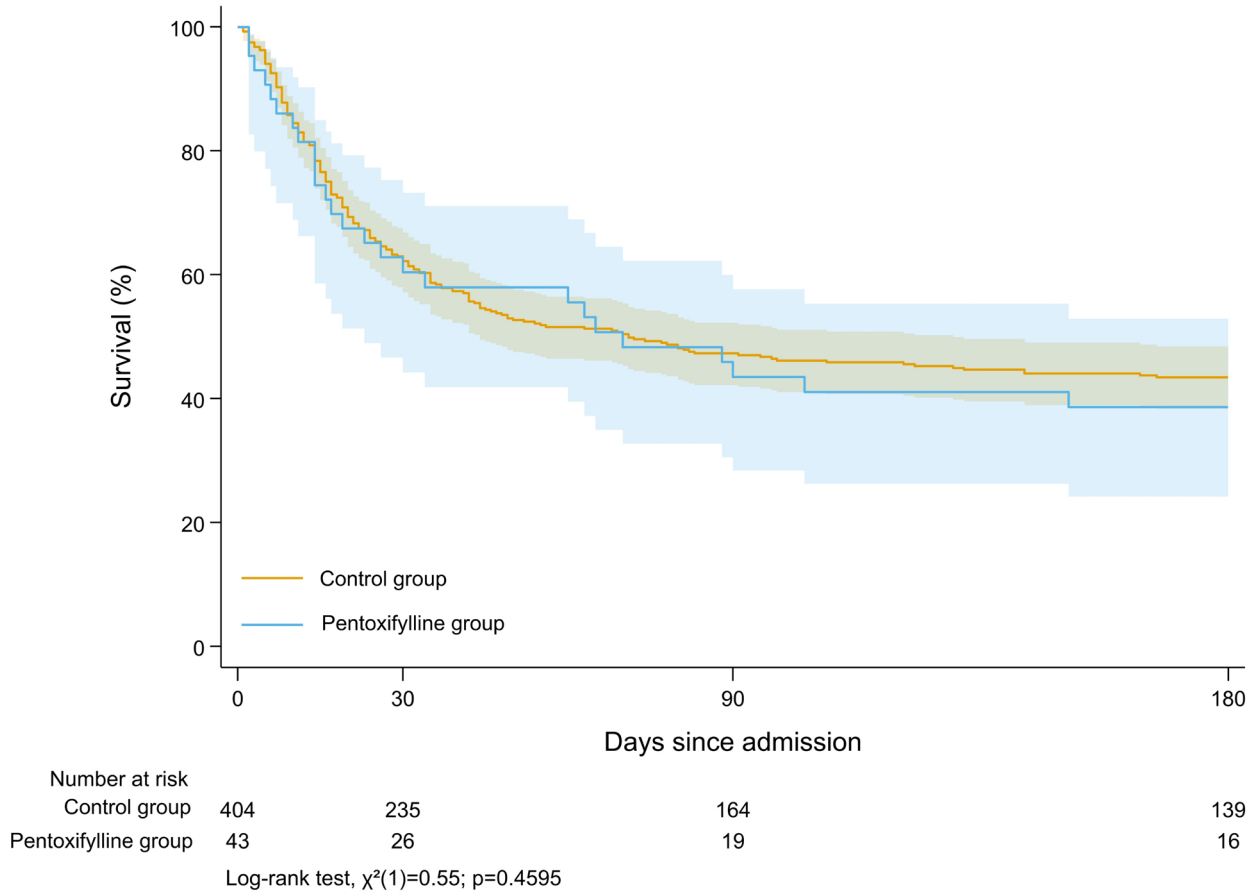

Figure 2 Kaplan-Meier curve of survival by pentoxifylline use in patients with creatinine greater than 1.5 mg/dL.

management strategies to improve survival in this high-risk population.

The high mortality observed in our study, particularly due to complications such as multiple organ failure, infections and renal failure, reflects the severity of the disease and the challenges involved in managing patients with sAH and AKI.[23] Despite advances in understanding the pathogenesis of sAH, therapeutic options remain limited, and there is a clear need for more effective treatments. This study reinforces the notion that while supportive care, including corticosteroids in patients with more severe disease, remains the cornerstone of management,

Table 4 Univariable and multivariable Cox regression models for time to death in patients with creatinine greater than 1.5 mg/dL

	Univariable analysis			Multivariable analysis		
Variables	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Pentoxifylline use	1.15	0.81 to 1.63	0.433	1.18	0.82 to 1.71	0.373
Gender	0.73	0.54 to 0.97	0.028	–		
Age	1.12	1.01 to 1.23	0.025	1.25	1.12 to 1.40	<0.001
Cirrhosis	1.01	0.74 to 1.39	0.941	–		
MELD score at admission	1.05	1.03 to 1.07	<0.001	1.06	1.04 to 1.08	<0.001
Use of corticosteroids	1.17	0.92 to 1.48	0.203	–		
Infection at admission	1.33	0.94 to 1.90	0.109	–		
Albumin at admission	0.81	0.68 to 0.96	0.013	–		
Creatinine at admission	1.08	1.01 to 1.14	0.021	–		
Total bilirubin at admission	1.01	1.00 to 1.02	0.046	–		
Renal replacement therapy	1.65	1.27 to 2.14	<0.001	1.41	1.06 to 1.87	0.017

HR, Hazard Ratio; MELD, Model for End-Stage Liver Disease.

additional therapeutic options are urgently needed to improve survival in this patient group.[24]

Our study has several limitations. As a retrospective registry-based analysis, this study is inherently prone to bias, particularly selection bias. Moreover, we were unable to evaluate the degree of alcohol abstinence achieved following hospitalisation or to include information on the initiation of therapy for AUD, which could affect long-term outcomes. The lack of data on the exact duration and timing of pentoxifylline treatment further limits the interpretation of our findings. Additionally, the significant percentage of missing data on infections (47.24%) introduces potential bias related to this variable, and the inclusion of this variable in the models may also lead to sample selection bias. Despite these limitations, our study contributes valuable data regarding the use of pentoxifylline in a real-world cohort of patients with sAH and AKI.

In conclusion, our study found that pentoxifylline does not improve survival in patients with sAH complicated by AKI. This suggests that pentoxifylline should not be recommended as a routine therapeutic option in this patient population. Further research is needed to identify more effective treatments for sAH and AKI, with a focus on novel pharmacological agents or combination therapies that can address the multifaceted pathophysiology of this condition. Until then, clinicians should continue to rely on established management strategies, including supportive care and early intervention for complications such as infections and renal failure, as the cornerstone of treatment in this high-risk group.

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REFERENCES

1 Aslam A, Kwo PY. Epidemiology and Disease Burden of Alcohol Associated Liver Disease. *J Clin Exp Hepatol* 2023;13:88–102.
2 Bataller R, Arab JP, Shah VH. Alcohol-Associated Hepatitis. *N Engl J Med* 2022;387:2436–48.
3 Arab JP, Roblero JP, Altamirano J, *et al*. Alcohol-related liver disease: Clinical practice guidelines by the Latin American Association for the Study of the Liver (ALEH). *Ann Hepatol* 2019;18:518–35.
4 Arab JP, Díaz LA, Baeza N, *et al*. Identification of optimal therapeutic window for steroid use in severe alcohol-associated hepatitis: A worldwide study. *J Hepatol* 2021;75:1026–33.
5 Thursz MR, Richardson P, Allison M, *et al*. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015;372:1619–28.
6 Akriviadis E, Botla R, Briggs W, *et al*. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637–48.
7 Lee Y-S, Kim HJ, Kim JH, *et al*. Treatment of Severe Alcoholic Hepatitis With Corticosteroid, Pentoxifylline, or Dual Therapy:

A Systematic Review and Meta-Analysis. *J Clin Gastroenterol* 2017;51:364–77.
8 Lebrec D, Thabut D, Oberti F, *et al*. Pentoxifylline does not decrease short-term mortality but does reduce complications in patients with advanced cirrhosis. *Gastroenterology* 2010;138:1755–62.
9 Mathurin P, O'Grady J, Carithers RL, *et al*. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011;60:255–60.
10 Blaney H, Díaz LA, Li N, *et al*. Global differences in the management of alcohol-associated hepatitis. *Lancet Gastroenterol Hepatol* 2024;9:972–4.
11 Hammerman C, Goldschmidt D, Caplan MS, *et al*. Amelioration of ischemia-reperfusion injury in rat intestine by pentoxifylline-mediated inhibition of xanthine oxidase. *J Pediatr Gastroenterol Nutr* 1999;29:69–74.
12 Okumura AS, Rodrigues LE, Martinelli R. Pentoxifylline in ischemia-induced acute kidney injury in rats. *Ren Fail* 2009;31:829–32.
13 Zhang M, Xu Y-J, Saini HK, *et al*. Pentoxifylline attenuates cardiac dysfunction and reduces TNF-alpha level in ischemic-reperfused heart. *Am J Physiol Heart Circ Physiol* 2005;289:H832–9.
14 Barkhordari K, Karimi A, Shafiee A, *et al*. Effect of pentoxifylline on preventing acute kidney injury after cardiac surgery by measuring urinary neutrophil gelatinase - associated lipocalin. *J Cardiothorac Surg* 2011;6:8.
15 Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, *et al*. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. *J Am Soc Nephrol* 2015;26:220–9.
16 Kuo K-L, Hung S-C, Liu J-S, *et al*. Add-on Protective Effect of Pentoxifylline in Advanced Chronic Kidney Disease Treated with Renin-Angiotensin-Aldosterone System Blockade - A Nationwide Database Analysis. *Sci Rep* 2015;5:17150.
17 Crabb DW, Bataller R, Chalasani NP, *et al*. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. *Gastroenterology* 2016;150:785–90.
18 Mehta RL, Kellum JA, Shah SV, *et al*. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
19 Altamirano J, Fagundes C, Dominguez M, *et al*. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. *Clin Gastroenterol Hepatol* 2012;10:65–71.
20 Singh SP, Khatua CR, Barik RK, *et al*. 1095 Presence of Acute Kidney Injury (AKI) at Admission in Severe Alcoholic Hepatitis (SAH) Patients Predicts Mortality: A Single Centre Experience. *Am J Gastroenterol* 2019;114:S618.
21 Khatua CR, Panigrahi MK, Choudhury AK, *et al*. Acute Kidney Injury (AKI) at Admission Predicts Mortality in Patients With Severe Alcoholic Hepatitis (SAH). *J Clin Exp Hepatol* 2023;13:225–32.
22 Sujan R, Cruz-Lemini M, Altamirano J, *et al*. A Validated Score Predicts Acute Kidney Injury and Survival in Patients With Alcoholic Hepatitis. *Liver Transpl* 2018;24:1655–64.
23 Ma AT, Allegretti AS, Cullaro G, *et al*. Outcomes of patients with alcohol-associated hepatitis and acute kidney injury - Results from the HRS Harmony Consortium. *Aliment Pharmacol Ther* 2024;60:778–86.
24 Idalsoaga F, Diaz LA, Ayares G, *et al*. Challenges in the management of alcohol-associated liver disease in Latin America. *Ann Hepatol* 2024;30:101748.