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Terlipressin use and respiratory failure in patients with hepatorenal syndrome type 1 and severe acute-on-chronic liver failure

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Summary

Background: Previous studies suggested increased mortality in patients with hepatorenal syndrome type 1 (HRS1) and advanced acute-on-chronic liver failure (ACLF).

Aim: To assess mortality and respiratory failure (RF) in patients with HRS1 and ACLF treated with terlipressin.

Methods: In the CONFIRM study, we randomised 299 patients with HRS1 2:1 to terlipressin or placebo, both with albumin. At enrolment, all patients were assessed for organ failure (OF) using a validated ACLF grading system. Post hoc analyses assessed the effects of terlipressin vs. placebo on the incidence of RF and 90-day mortality.

Results: The incidence of RF with terlipressin ($n = 200$) was 9.4% in patients with grades 1–2 ACLF, and 30% with grade 3 ACLF ($p = 0.0002$); no such difference was observed in placebo-treated patients ($n = 99$) (6.2% grades 1–2 vs. 0% grade 3 ACLF, $p > 0.05$). RF incidence between terlipressin and placebo in patients with grade 3 ACLF was significant ($p = 0.01$). Baseline predictors of RF with terlipressin were INR ($p = 0.011$), mean arterial pressure ($p = 0.037$), and SpO_2 ($p = 0.014$). Prior albumin as a continuous variable was not a predictor of RF. 90-day survival between terlipressin and placebo arms was similar for grades 1–2 ACLF (55.5% and 56.6%, respectively), but lower for grade 3 ACLF (27.55% vs. 50.0%) ($p = 0.122$), mainly related to RF.

Conclusion: Terlipressin should be used with caution in patients with HRS1 and grade 3 ACLF. Patients with hypoxaemia are at increased risk of RF and mortality.

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1 | INTRODUCTION

Hepatorenal syndrome type 1 (HRS1) is a severe complication of liver cirrhosis with ascites. It is a special form of acute kidney injury (AKI), defined as an acute rise in serum creatinine (sCr) to ≥2.5 mg/dl in less than 2 weeks when all other known causes of AKI have been excluded,[1] associated with poor survival of a few weeks if left untreated.[2] One of the major pathophysiological mechanisms involved in the development of HRS1 is splanchnic and systemic vasodilatation leading to paradoxical renal vasoconstriction.[3] Therefore, the mainstay of treatment for HRS1 is the use of systemic and/or splanchnic vasoconstrictors.[4] Terlipressin is the most widely used splanchnic vasoconstrictor for the treatment of HRS1 worldwide.[5] The recent publication of the results of the CONFIRM trial (ClinicalTrials.gov identifier: NCT02770716),[6] which assessed the effects of terlipressin versus placebo, both with albumin, in the treatment of HRS1 in cirrhosis and ascites, reported an increased incidence of respiratory failure in patients who received terlipressin, but not in those who received placebo. The incidence of respiratory failure appeared to be most common among very ill patients, especially those with high-grade acute-on-chronic liver failure (ACLF).

ACLF is a newly recognised syndrome that is observed in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and high short-term mortality within 4 weeks.[7] The European Association for the Study of the Liver (EASL) defines ACLF by the number of organ failures in any of six organ systems as described by the modified Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score.[8] The ACLF severity is then graded according to the number of organ failures.[8] ACLF is common in patients with HRS1. In addition to liver and kidney failures, non-hepatic organ dysfunction has been described in patients with AKI.[9,10] Furthermore, the occurrence of grade 1 ACLF, which all patients with HRS1 have, confers a higher risk for subsequent higher grade ACLF development when compared with patients who have never developed ACLF.[11] The use of terlipressin, which increases the systemic vascular resistance and cardiac afterload, may affect cardiac and respiratory function, especially in cirrhotic patients with advanced ACLF and who may have underlying cirrhotic cardiomyopathy. In this post-hoc analysis of the CONFIRM trial, we aimed to evaluate mortality in patients with HRS1 and baseline grade 3 ACLF versus grades 1–2 ACLF and identify risk factors for the development of respiratory failure with terlipressin use.

2 | PATIENTS AND METHODS

The protocol for the CONFIRM double-blind placebo-controlled trial has previously been published.[6] In brief, patients who were at least 18 years of age, with cirrhosis, ascites, and rapidly progressive renal failure, with an sCr doubling to at least 2.25 mg/dl within 14 days who showed minimal response with ≤20% reduction in sCr after at least 48 h of diuretic withdrawal and plasma volume expansion with albumin, were included. Patients were excluded if they had an sCr of >7.0 mg/dl, one or more large volume paracenteses of ≥4 L within 2 days of randomisation, presence of shock, or sepsis and/or uncontrolled bacterial infection. Once enrolled, patients were randomly assigned to receive in 2:1 ratio of terlipressin or placebo 1 mg every 6 h by slow intravenous bolus injections under close observation. If sCr reduction was less than 30% from the baseline value on day 4, after a minimum of 10 doses of study drug, the dose could be increased to 2 mg every 6 h, except in patients with coronary artery disease, circulatory overload, pulmonary edema, or bronchospasm. Dose resumption was permitted after interruption for adverse events (AEs) except for cardiac or mesenteric ischemia, for which treatment was permanently discontinued. Patients were recommended to receive concomitant albumin at a dose of 20–40 gm/day as clinically indicated.

Patients were assessed for the presence of ACLF at study entry as described by the EASL-CLIF criteria.[8] All patients had minimum grade 1 ACLF, because all had an sCr of ≥2 mg/dl due to the presence of HRS1. Grade 2 and 3 ACLF represented two and three organ failures, respectively.[8] Patients were divided into those with grades 1–2 versus grade 3 ACLF and compared. Patients were monitored for AEs up to 7 days and serious adverse events (SAEs) up to 30 days after completion of treatment. The primary efficacy end point of the CONFIRM study was verified HRS reversal, defined as the percentage of patients with two consecutive sCr values no greater than 1.5 mg/dl at least 2 h apart, while on treatment (up to 24 h after the last dose) by Day 14 or discharge, and remaining alive without renal replacement therapy for at least 10 days. The end points of this study were the development of respiratory failure as an SAE (using the terms “acute respiratory failure” or “respiratory failure”) as reported by study site principal investigators, and mortality up to 90 days post treatment.

2.1 | Statistical analysis

Continuous data were compared using a *t*-test. Binary and categorical data were analysed using a Cochran–Mantel–Haenszel (CMH) chi-square test, chi-square test, or a Fisher Exact test as follows: a CMH chi-square test stratified by qualifying sCr (less than 3.4 mg/dl or at least 3.4 mg/dl) and pre-enrolment large volume paracentesis (at least one single event of at least 4 L or less than 4 L within 3 to 14 days before randomisation) if the number of events per cell and the number of expected events per cell were at least 5. If the expected cell counts were less than 5, an unstratified chi-square test was used instead of the CMH test. If the number of events per cell was less than 5, then a Fisher Exact test was used. Overall survival up to 90 days, defined as the days that each subject survived from the day of randomisation, was analysed using a two-sample log rank test. Predictors of respiratory failure were determined by first evaluating which baseline parameters were significant in univariate logistic regression models for respiratory failure. Then multivariate logistic regression with stepwise selection was used to determine

the final significant baseline parameters. To assess competing risks, cumulative incidence function (CIF) estimates of the marginal probability for each competing event (cause-specific hazards of death or transplant) were calculated using Gray's test.[12]

3 | RESULTS

Between July 13, 2016 and July 24, 2019, 300 patients with HRS1 were enrolled into the CONFIRM trial, with 199 patients randomly assigned to receive terlipressin and 101 patients to receive placebo. At study entry, all patients had renal failure as defined by the EASL-CLIF-SOFA score and therefore had at least grade 1 ACLF, and no patient had circulatory failure because these were excluded for enrolment. Similar distribution of ACLF grades was observed between the terlipressin and placebo groups, grade 1: $n = 99$ or 49.5% for terlipressin and $n = 41$ or 41.4% for placebo; grade 2: $n = 61$ or 30.5% for terlipressin and $n = 40$ or 40.4% for placebo; grade 3: $n = 40$ or 20.0% for terlipressin and $n = 18$ or 18.2% for placebo. Table 1 shows patient demographics, vital signs, and laboratory data at study entry between the various subgroups.

3.1 | Types of organ failure

The prevalence of various organ failures at baseline is shown in Table 1. All patients had renal failure at entry into the study. The next most common organ failure was liver failure, followed by coagulation failure, cerebral failure, and respiratory failure. The number of patients improving from baseline ACLF grade 3 to ACLF grade 0, 1, or 2 with treatment was similar between the terlipressin and placebo groups (Table S1).

One of the secondary end points of the CONFIRM study was reversal of HRS, defined as any serum creatinine level of 1.5 mg/dl or less; this was observed in 36.2% of patients who received terlipressin, and 16.8% of patients who received placebo ($p < 0.001$) at the end of treatment.[6] When patients were separated into grades 1–2 and grade 3 ACLF subgroups, there was a significant difference in the rates of HRS reversal in the grades 1–2 ACLF versus the grade 3 ACLF subgroup ($p = 0.0007$; Figure 1). The use of terlipressin was only able to achieve an increased HRS reversal rate versus placebo in the grades 1–2 ACLF subgroup ($p = 0.0002$), but this was not observed in the grade 3 ACLF subgroup (Figure 1).

3.2 | Respiratory failure

Respiratory (lung) failure as defined by EASL-CLIF-SOFA score criteria[8] was found at baseline in five (2.5%) patients who received terlipressin and in three (3.0%) patients who received placebo (Table 1). At the end of treatment, in the terlipressin group, there were significantly more patients ($n = 16$, 8.0%) who developed respiratory failure as defined by EASL-CLIF-SOFA score criteria, when compared with baseline ($p = 0.023$); in the placebo group, there was no difference in the number of patients with respiratory failure defined by EASL-CLIF-SOFA score criteria at the end of treatment compared with baseline (Figure 2A).

Respiratory failure during treatment and follow-up periods was reported as AEs or SAEs by the study investigators; based on individual patient review, there were no clinically meaningful differences between the characteristics of patients with reported "acute respiratory failure" versus "respiratory failure." Accordingly, the two safety terms were combined and are referred to in this paper as "respiratory failure." The incidence of respiratory failure as reported by study investigators up to 30 days post treatment for both study groups, separated by patients with grades 1–2 ACLF versus grade 3 ACLF groups, is shown in Figure 2B. Within the terlipressin group, a significantly greater number of patients with grade 3 ACLF developed respiratory failure ($n = 12/40$, 30%) compared with those patients with grades 1–2 ACLF ($n = 15/160$, 9.4%, $p = 0.002$). Among those in the grade 3 ACLF subgroup, there were significantly more patients who received terlipressin and developed respiratory failure ($n = 12/40$, 30%), when compared with those who received placebo ($n = 0/18$, 0%, $p = 0.01$; Figure 2B).

There was also a significantly greater number of deaths up to 30 days post treatment attributed to respiratory failure among patients with grade 3 ACLF who received terlipressin ($n = 9/40$, 22.5%) versus placebo ($n = 0/18$, 0%, $p = 0.05$; Figure 2C).

The time to onset of, and time to death from, respiratory failure was approximately 5 to 7 days and 14 days, respectively, in both treatment groups. Based on individual patient review, a history of recent, baseline, or treatment-emergent dyspnea, pneumonia/ aspiration pneumonia, grade 3 or increasing hepatic encephalopathy, or upper gastrointestinal haemorrhage was present in most patients who developed respiratory failure in both treatment groups.

3.3 | Predictors of respiratory failure

Among various baseline characteristics, univariate logistic regression analysis identified baseline grade 1–2 versus grade 3 ACLF as a significant predictor of respiratory failure among patients who received terlipressin (intent-to-treat population; $p = 0.002$), but not for those who received placebo (Table S2). When multivariate logistic regression analysis was done using all significant univariate results, we found that baseline international normalised ratio (INR), mean arterial pressure (MAP), and pulse oximeter oxygen saturation (SpO_2) were significant predictors of respiratory failure among patients who received terlipressin (Table 2). Prior albumin as a continuous variable was not a predictor of respiratory failure in the CONFIRM study.No predictors were identified for the placebo population.

Because some cases of respiratory failure were associated with volume overload, the amount of albumin given before study enrolment was further assessed by determining the incidence of respiratory failure in the terlipressin and placebo groups by quartiles of albumin amounts given before enrolment into the study (Table 3).

TABLE 1 Baseline patient demographics, vital signs, and laboratory data

Parameter	ACLF grades 1–2 ($n = 241$)			ACLF grade 3 ($n = 58$)		
	Terlipressin ($n = 160$)	Placebo ($n = 81$)	p value[d]	Terlipressin ($n = 40$)	Placebo ($n = 18$)	p value[d]
Age (years), mean ± SD	55.7 ± 11.0	54.6 ± 11.7	0.483	47.6 ± 10.8	47.8 ± 10.8	0.962
Male:Female, *n*	94:66	48:33	0.999	26:14	10:8	0.374
Aetiology of cirrhosis, *n* (%)						
Alcohol	101 (63.1)	52 (64.2)	0.888	33 (82.5)	15 (83.3)	1.000
Viral hepatitis	28 (17.5)	4 (4.9)	0.007	6 (15.0)	4(22.2)	0.483
NASH	39 (24.4)	20 (24.7)	1.000	3 (7.5)	3 (16.7)	0.362
Auto-immune	6 (3.8)	3 (3.7)	1.000	5 (12.5)	1 (5.0)	0.655
Primary biliary Cholangitis	4 (2.5)	3 (3.7)	0.690	1 (2.5)	0 (0.0)	1.000
Cryptogenic	4 (2.5)	3 (3.7)	0.690	2 (5.0)	0 (0.0)	1.000
Other	8 (5.0)	5 (6.2)	0.766	1 (2.5)	0 (0.0)	1.000
Comorbid conditions, *n* (%)						
Diabetes[a]	40 (25.0)	26 (32.1)	0.245	13 (32.5)	3 (16.7)	0.342
Systemic hypertension[b]	62 (38.8)	28 (34.6)	0.468	11 (27.5)	7 (38.9)	0.529
SIRS, *n* (%)	63 (39.4)	35 (43.2)	0.501	22 (55.0)	12 (66.7)	0.254
Alcoholic hepatitis, *n* (%)	56 (35.0)	27 (33.3)	0.791	25 (62.5)	12 (66.7)	0.465
Cirrhosis complications, *n* (%)						
History variceal bleed	22 (13.8)	17 (21.0)	0.194	8 (20)	3 (16.7)	1.000
History hepatic encephalopathy	97 (60.6)	60 (74.1)	0.049	26 (65.0)	11 (61.1)	0.989
Infection prior to 14 days[c], *n* (%)	67 (41.9)	37 (45.7)	0.485	21 (52.5)	11 (61.1)	0.204
Type of organ failure, *n* (%)						
Renal	160 (100.0)	81 (100.0)	N/A	40 (100.0)	18 (100.0)	N/A
Coagulation	24 (15.0)	11 (13.6)	0.707	35 (87.5)	16 (88.9)	1.000
Liver	33 (20.6)	27 (33.3)	0.024	37 (92.5)	17 (94.4)	1.000
Cerebral	3 (1.9)	2 (2.5)	1.000	10 (25.0)	4 (22.2)	1.000
Respiratory	1 (0.6)	0	1.000	4 (10.0)	3 (16.7)	0.665
Child-Pugh score, mean ± SD *n*	9.6 ± 1.8 156	10.0 ± 1.9 77	0.166	11.6 ± 1.3 39	11.6 ± 1.5 16	0.930
MELD score, mean ± SD, *n*	30.8 ± 6.3 138	31.6 ± 5.8 68	0.418	39.2 ± 1.8 40	38.3 ± 4.7 18	0.487
Heart rate (bpm), mean ± SD	77.8 ± 15.8	82.0 ± 15.1	0.051	84.9 ± 14.3	90.9 ± 12.1	0.128
MAP (mmHg), mean ± SD	77.6 ± 11.8	77.4 ± 9.4	0.899	82.9 ± 12.2	79.1 ± 9.0	0.247
Respiratory rate (breaths/min), mean ± SD	17.8 ± 3.2	17.5 ± 2.8	0.465	18.6 ± 2.9	17.9 ± 3.1	0.405
SpO_2/FiO_2, mean ± SD, *n*	450 ± 60 98	440 ± 60 58	0.413	400 ± 130 24	390 ± 130 12	0.870
Haemoglobin (g/dl), mean ± SD, *n*	8.7 ± 1.9 155	9.9 ± 13.2 80	0.421	8.6 ± 2.6 40	8.0 ± 1.1 18	0.227
White blood cell count ($\times 10^9$/L), mean ± SD, n	8.9 ± 6.1 153	8.7 ± 5.2 79	0.847	11.3 ± 5.0 40	11.4 ± 6.2 18	0.905
INR, mean ± SD, *n*	2.0 ± 0.7 142	2.0 ± 0.6 69	0.648	3.1 ± 0.9 40	4.3 ± 5.2 18	0.342
Sodium (mmol/L), mean ± SD *n*	133.1 ± 5.5 157	133.0 ± 5.2 80	0.945	133.2 ± 6.0 40	134.7 ± 6.9 18	0.406
Potassium (mmol/L), mean ± SD, *n*	4.2 ± 0.7 156	4.2 ± 0.7 80	0.550	3.9 ± 0.6 40	3.9 ± 0.6 18	0.951

(Continues)

TABLE 1 (Continued)

Parameter	ACLF grades 1–2 ($n = 241$)			ACLF grade 3 ($n = 58$)		
	Terlipressin ($n = 160$)	Placebo ($n = 81$)	p value[d]	Terlipressin ($n = 40$)	Placebo ($n = 18$)	p value[d]
Serum creatinine (mg/dl), mean ± SD, n	3.5 ± 1.0 160	3.5 ± 1.0 81	0.826	3.5 ± 0.9 40	3.4 ± 0.9 18	0.734
Total bilirubin (mg/dl), mean ± SD, n	9.4 ± 11.3 149	11.7 ± 12.5 79	0.151	27.1 ± 12.2 40	29.2 ± 19.8 18	0.683
Albumin (g/dl), mean ± SD, n	3.8 ± 0.7 148	4.1 ± 2.9 77	0.248	3.5 ± 0.8 40	3.6 ± 0.7 18	0.498

Abbreviations: ACLF, acute-on-chronic liver failure; BPM, beats per minute; CMH, Cochran–Mantel–Haenszel; INR, international normalised ratio; LVP, large volume parenteral; MAP, mean arterial pressure; MELD, model for end stage liver disease; min, minute; N/A, not applicable; NASH, non-alcoholic steatohepatitis; sCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO_2/FiO_2, oxygen saturation to fraction of inspired oxygen ratio.

[a]Includes medical history of diabetes, diabetes mellitus, and type 2 diabetes mellitus.

[b]Includes medical history terms of hypertension and systemic hypertension.

[c]Prior infection includes events of spontaneous bacterial peritonitis, urinary tract infection, pneumonia, and others occurring 14 days prior to randomisation.

[d]Continuous data are compared using a t-test. For binary and categorical data: If the number of expected events per cell and the number of events per cell are at least 5, a CMH test stratified by qualifying sCr (<3.4 vs >=3.4 mg/dl) and LVP within 14 days of randomisation (at least one single event of >=4 vs <4 L) is used. If the number of expected events per cell is less than 5 in one or more cells and the number of events per cell is at least 5, then a chi-square test is used. If the number of expected events per cell is less than 5 in one or more cells and the number of events per cell is less than 5 in one or more cells, then a Fisher's Exact test is used.

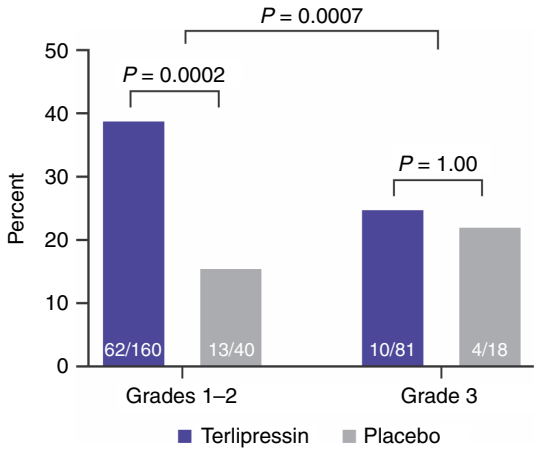


FIGURE 1 Renal failure reversal by ACLF grade with terlipressin versus placebo. ACLF, acute-on-chronic liver failure.

This analysis did not indicate a clear relationship between the incidence of respiratory failure and the amount of albumin prior to terlipressin or placebo administration. Similarly, prior albumin as a continuous variable was not a predictor of respiratory failure in the terlipressin or placebo groups (Table S3).

3.4 | Mortality

At the end of the 90-day follow-up after completion of treatment, there were 101 deaths (50.8%) in the terlipressin group and 45 deaths (44.6%) in the placebo group. Although the overall and transplant-free survival does not differ between the terlipressin and placebo groups,[6] subcategories of ACLF grades were used to assess mortality given that there were increased deaths from respiratory failure in patients with grade 3 ACLF who received terlipressin. Figure 3 shows that there was no difference in mortality between the terlipressin and placebo subgroups in those patients with grades 1–2 ACLF. However, in the terlipressin group, mortality was significantly higher in patients with grade 3 ACLF versus those with grades 1–2 ACLF ($p < 0.001$; Figure 3). Overall survival to 90 days in patients with baseline ACLF grade 1a (kidney failure-HRS only) was similar in the terlipressin and placebo groups, p = 0.7183 (Figure S1). Competing risk analysis indicated that in patients with baseline ACLF grade 3, there was a significant difference in the CIF estimates for the competing events of transplant or death for terlipressin compared to placebo (Gray's p = 0.039); for patients with ACLF < grade 3, there was no significant impact of treatment on CIF estimates for those competing events (Gray's p = 0.780) (Figures S2 and S3). Time to transplant by baseline ACLF grade was similar between treatment groups (Table S4).

3.5 | Other adverse events

Although respiratory failure was the most common SAE reported in patients with grade 3 versus grades 1–2 ACLF in the terlipressin group, there was less of an imbalance between terlipressin and placebo treatment for other reported SAEs. In patients with grade 3 ACLF, multiple organ dysfunction syndrome and sepsis appeared to be slightly more common in the terlipressin group, with hepatic failure and alcoholic cirrhosis being more commonly reported in the placebo group; these trends were present for both overall SAEs reported as well as AEs leading to death (see Tables S5 and S6).

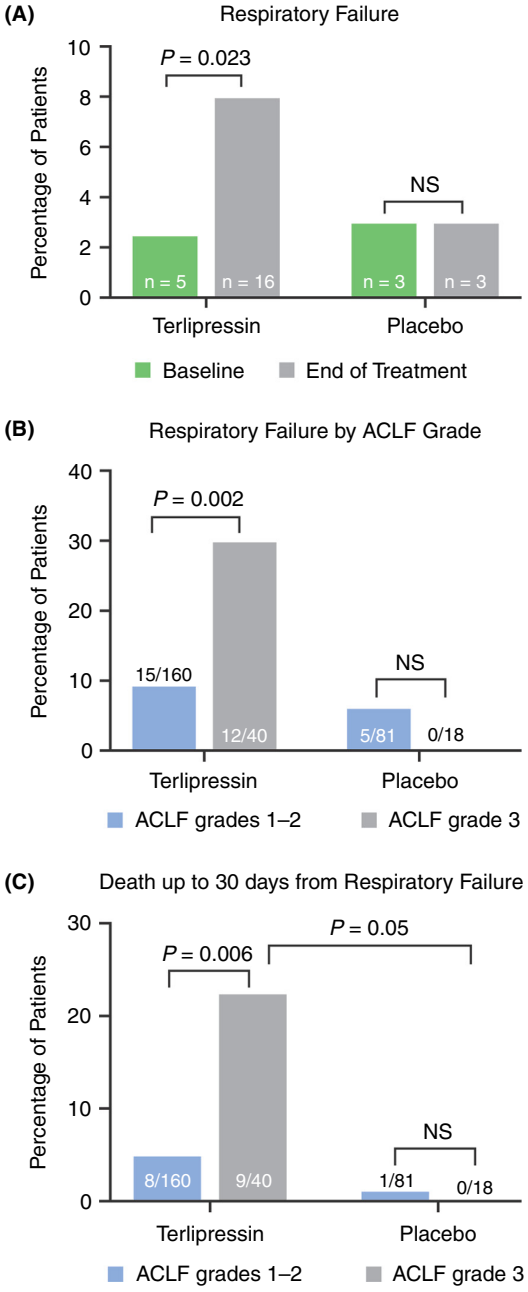


FIGURE 2 (A) Percentage of patients with baseline and end-of-treatment CLIF-SOFA defined respiratory failure, Terlipressin, and placebo groups (ITT population); (B) Percentage of patients with respiratory failure serious adverse events up to 30 days post treatment by treatment group and baseline ACLF grade (safety population); (C) Percentage of patients with respiratory failure SAEs leading to death up to 30 days post treatment by treatment group and baseline ACLF grade (safety population). ACLF, acute-on-chronic liver failure; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; ITT, intent-to-treat; NS, not significant; SAEs, serious adverse events.

4 | DISCUSSION

The results of this retrospective study, utilising data from the largest randomised, placebo-controlled study for the evaluation of terlipressin treatment for HRS1, expand on our previous report that terlipressin is more effective than placebo in improving renal function but is associated with SAEs, including respiratory failure.[6] Our findings comport with previous publications indicating that terlipressin, when used for the treatment of HRS1, is associated with decreased overall survival in patients with grade 3 ACLF[13] and provide placebo-controlled data that this is mainly related to respiratory failure in this subpopulation of patients; survival in patients with grades 1–2 ACLF treated with terlipressin is similar to that for placebo. Patients with grade 3 ACLF treated with terlipressin are at an increased risk of developing respiratory failure compared with those treated with placebo. Higher baseline INR, MAP, and a lower baseline SpO_2 are risk factors for the development of respiratory failure with terlipressin therapy. This latter observation suggests that pre-existing, or treatment-emergent hypoxaemia and pulmonary dysfunction identifies a population of patients who may be particularly at risk for developing respiratory failure with terlipressin. Careful monitoring for the development of circulatory overload, assessment of baseline or treatment-emergent impaired oxygenation with SpO_2 monitoring, and avoiding excessive use of albumin infusions appear to be important strategies that are likely to be valuable to mitigate the development of respiratory failure in patients with HRS1 treated with terlipressin.

Terlipressin, a vasopressin analogue, has been shown to be effective in the management of HRS1 in cirrhosis.[6,14–16] Although ischemic side effects have been uncommonly, but regularly observed in patients receiving terlipressin,[17] respiratory failure as a complication of terlipressin has not been commonly reported or characterised. In a Cochrane systematic review in 2012, circulatory overload and respiratory distress or acidosis was briefly reported in seven and three patients, respectively, based on two small studies that formed part of the review.[17] In the CONFIRM study and this more detailed analysis, respiratory failure is reported as an important potential AE for terlipressin. This is likely related in part to the fact that the CONFIRM study was the largest clinical trial in patients with HRS1 with a rigorous safety assessment and the greatest number of patients exposed to terlipressin, with terlipressin dosing and duration of treatment (approximately 6 days) similar to previous terlipressin studies.[15,16] Although there were safety signals from prior studies, the larger CONFIRM study has allowed a more meaningful description of the incidence and impact of respiratory failure with terlipressin, particularly in patients with advanced disease or grade 3 ACLF.

The effects of terlipressin on cardiopulmonary hemodynamics are complicated and the precise mechanisms leading to respiratory failure in patients with cirrhosis and HRS1 who receive terlipressin are unclear. Terlipressin is known to have differential effects on pulmonary versus the systemic hemodynamics.[18] In patients with cirrhosis but without underlying portopulmonary hypertension or cardiac disease, a single dose of 2 mg of intravenous terlipressin was noted to induce an increase in pulmonary arterial pressure; in contrast, in patients with cirrhosis and pulmonary hypertension, the same single dose is associated with a decrease in pulmonary arterial pressure.[18] A 2 mg dose of terlipressin has been shown to decrease heart rate and lead to a reduction in cardiac output.[19] It is

TABLE 2 Multivariate logistic regression analysis of baseline characteristics on respiratory failure reported as a serious adverse event (ITT population)

	Respiratory failure serious adverse events				
	Terlipressin				Placebo
Baseline Parameters[a]	*n*	Odds ratio	95% Confidence intervals	*p* value	
INR	179	1.810	1.149–2.852	0.011	There are no significant results
MAP	179	1.037	1.002–1.072	0.037	
SpO_2	179	0.835	0.722–0.965	0.014	

Notes: Respiratory failure includes acute respiratory failure and respiratory failure.

n = number of patients in the model.

Abbreviations: INR, International normalised ratio; ITT, intent-to-treat; MAP, mean arterial pressure; SpO_2, pulse oximeter oxygen saturation.

[a]All significant univariate results were added to the model and stepwise selection was used to obtain the final model.

TABLE 3 Respiratory failure serious adverse events by quartiles of prior albumin

Quartiles of prior albumin (g)	Incidence of respiratory failure *n/N* (%)[a]	
	Terlipressin	Placebo
≤218.75 g	5/50 (10%)	1/24 (4.2%)
>218.75 g to ≤325 g	9/59 (15.3%)	2/23 (8.7%)
>325 g to ≤450 g	10/53 (18.9%)	1/24 (4.2%)
>450 g	4/36 (11.1%)	1/27 (3.7%)

Notes: *N* = number of patients in the study, treatment group, and prior albumin category. *n* = number of patients with respiratory failure SAEs in the category of patients in the study, treatment group, and prior albumin category.

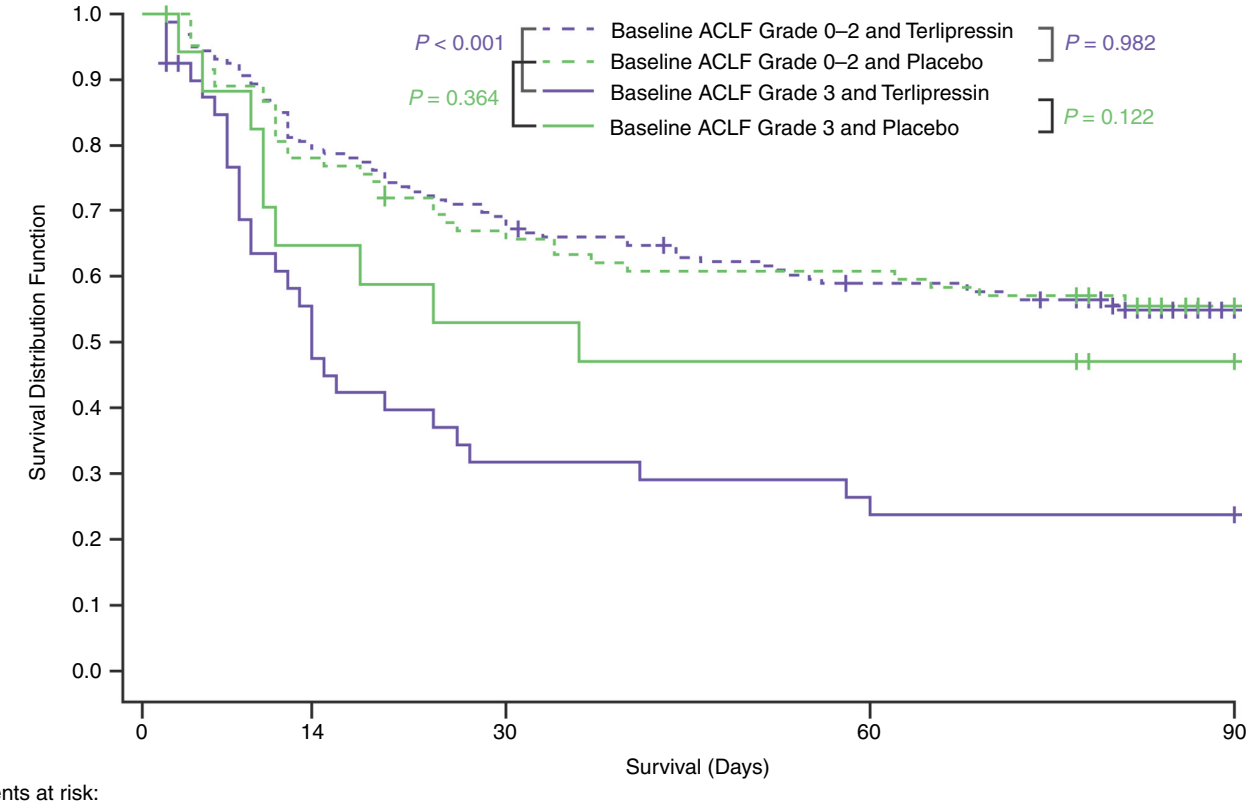
Abbreviation: SAEs, serious adverse events.

[a]Respiratory failure SAEs include respiratory failure and acute respiratory failure SAEs.

likely that the combined effects of terlipressin on cardiac function and pulmonary hemodynamics lead to congestion in the pulmonary circulation and hypoxaemia in some patients. In a study reassessing four cohorts of patients with HRS1 who received terlipressin within previous trials,[13] while no cases of respiratory failure were specifically reported, 20 of 241 patients had a reported side effect of circulatory overload, suggesting the cardiopulmonary effects of terlipressin may contribute to, or be exacerbated by, volume overload in these patients. The observation of a trend for an increased incidence of respiratory failure among the patients who received an increasing dose of albumin prior to receiving terlipressin (Table 3) further suggests that volume overload from the albumin could unmask the cardiac and pulmonary effects of terlipressin. In summary, patients with decompensated cirrhosis may have compromised respiratory function at baseline. Terlipressin, by increasing cardiac afterload and effective circulating volume, may affect cardiac systolic and diastolic function, leading to compromised pulmonary function, particularly in the setting of fluid overload.[18,20]

In addition to the direct cardiopulmonary effects of terlipressin, the increased incidence of respiratory failure in patients with grade 3 ACLF are likely in part related to the existence of underlying severe ACLF. Cirrhosis is known to be an inflammatory state; the more advanced the cirrhosis, the more severe the extent of inflammation.[21] In patients with high grades of ACLF, measurements of various inflammatory cytokines and chemokines suggest that the inflammation is very intense and associated with mitochondrial dysfunction and altered microcirculation.[22] This hyperinflammatory state ultimately impairs the host immune defence mechanisms, rendering patients with ACLF more vulnerable to secondary infections, increased organ dysfunction, and increased mortality. It is not unexpected that organ failures such as respiratory failure would be more common in patients with grade 3 ACLF even in the absence of terlipressin, possibly related to excessive damage -associated molecular patterns (DAMPS) that fuel an inflammatory cascade that can initiate or perpetuate other organ dysfunction.[23] In patients with grade 3 ACLF, the combined cardiac suppressive and pulmonary arterial hypertensive effects of terlipressin in some patients, together with volume overload related to excess albumin, creates "a perfect storm" for respiratory failure to develop within a hyperinflammatory state.

It has been suggested that the use of terlipressin for the treatment of HRS in cirrhosis be avoided in patients with grade 3 ACLF, especially those patients with baseline predictors; this is also the group of patients who are less likely to respond with reversal of HRS (Figure 1).[12] As observed in this patient population, multiple organ failures with a high grade of ACLF may be providing a constant source of pro-inflammatory cytokines, which perpetuate renal injury rendering patients unresponsive to terlipressin-related improved renal hemodynamics.[13,24] However, a small number of patients with high-grade ACLF do respond to terlipressin with reversal of HRS1.[25] Accordingly, it may be reasonable to carefully start terlipressin treatment in highly selected patients with HRS and advanced ACLF, if they do not have competing cardiopulmonary comorbidities and recent hypoxaemia and in whom liver transplantation may not be an option.[25] Particularly, careful monitoring for the development of respiratory failure in this group of patients would be important; a detailed discussion with the patient and their family of the risk-benefits of terlipressin treatment in this setting are strongly suggested. ACLF is a dynamic event, which can improve with treatment. It has been suggested that terlipressin be administered in these



Patients at risk:

ACLF 0–2, Terli	159	128	110	91	56
ACLF 0–2, Placebo	83	64	54	49	28
ACLF 3, Terli	40	21	12	10	9
ACLF 3, Placebo	18	11	9	8	6

FIGURE 3 Mortality in patients up to 90 days by treatment group and baseline ACLF grade (safety population). ACLF, acute-on-chronic liver failure.

selected patients for 3 days, especially in patients who are young, with vigilant monitoring for signs of improvement or deterioration.[25] Otherwise, treatment options for these patients are very limited, especially if liver transplantation is not available.

In conclusion, the use of terlipressin, together with albumin, in the treatment of HRS1 with cirrhosis can lead to the development of respiratory failure. This is especially true in patients with advanced grade 3 ACLF. All patients receiving terlipressin need to be monitored closely for the development of respiratory failure; excessive use of albumin should be avoided. Future studies should focus on elucidating the precise mechanisms involved in the development of respiratory failure associated with terlipressin treatment, the inflammatory components that may be active, treatment algorithms to mitigate adverse events, and the evaluation of new treatments for these severely ill patients.

AUTHOR CONTRIBUTIONS

Florence Wong: Conceptualization (lead); data curation (equal); investigation (equal); methodology (equal); writing – original draft (lead); writing – review and editing (lead). **Stephen Chris Pappas:** Conceptualization (lead); data curation (lead); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (lead). **Rajender Reddy:** Data curation (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Hugo E. Vargas:** Data curation (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Michael P. Curry:** Data curation (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Arun J. Sanyal:** Data curation (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Khurram Jamil:** Funding acquisition (lead); writing – review and editing (supporting).

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SUPPORTING INFORMATION

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

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