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Defining Renal Recovery in Patients With Hepatorenal Syndrome-Acute Kidney Injury: Experience From North American Studies

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ABSTRACT

Introduction: The degree of improvement in serum creatinine (SCr) has previously been suggested as a sensitive indicator of treatment response in patients with hepatorenal syndrome-acute kidney injury (HRS-AKI), while HRS reversal remains the primary endpoint in clinical trials.

Methods: A total of ≥30% SCr improvement was analyzed as an exploratory prespecified endpoint in the CONFIRM trial. In this post hoc analysis, intent-to-treat population data from three Phase 3 studies (OT-0401, REVERSE, and CONFIRM) conducted in North America in patients with HRS-AKI were pooled to assess the incidence of >30% improvement in SCr and its association with clinical outcomes.

Results: Significantly more patients treated with terlipressin achieved >30% improvement in SCr compared with those who received a placebo (42.9% vs. 23.4%; $p < 0.001$). Compared with patients who did not achieve >30% improvement in SCr, those who achieved this threshold had a lower incidence of renal replacement therapy (RRT) (55.2% vs. 14%, respectively; $p < 0.001$) and greater overall survival at Day 90 (41.6% vs. 71.1%, respectively; $p < 0.001$); a greater proportion achieved durability of HRS reversal (1% [95% confidence interval, 95% CI: 0] vs. 68.9% [95% CI: 0.6, 0.8]) and more patients were alive without RRT (22.7% vs. 61.6%, respectively; $p < 0.001$) or transplant (11.6% vs. 43.0%, respectively; $p < 0.0001$). Additionally, the overall survival and RRT-free survival in the group that achieved >30% improvement in SCr without HRS reversal were comparable to the overall group that achieved HRS reversal.

Conclusion: A total of >30% improvement in SCr levels even without HRS reversal may serve as a clinically meaningful endpoint to define renal recovery in patients with HRS-AKI.

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1 | Introduction

1.1 | Overview of Hepatorenal Syndrome (HRS) and Diagnostic Criteria for Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI)

HRS-AKI is a rapidly progressive and potentially reversible kidney injury in patients with decompensated cirrhosis associated with high mortality if not diagnosed and treated promptly [1, 2]. The definitions of AKI and HRS in patients with cirrhosis have evolved over the past decades [3–6]. HRS was previously classified as either type 1 (HRS-1) or type 2 (HRS-2), with HRS-1 characterized by a rapid deterioration of renal function by doubling of serum creatinine (SCr) level to > 2.5 mg/dL in < 2 weeks, and HRS-2, defined as a more chronic deterioration in kidney function [3]. In 2015, the International Club of Ascites (ICA) revised the diagnostic criteria of HRS-1 to include AKI as a diagnostic parameter, defined as an increase in SCr of ≥ 0.3 mg/dL within 48 h and/or a ≥ 50% increase from baseline, and renamed the condition HRS-AKI [5, 6]. The original definition of HRS-1 required that the diagnosis be established at an advanced stage of AKI, whereas the updated definition of HRS-AKI facilitates the early treatment of patients even with modest increases in SCr levels [5–7].

1.2 | Defining Renal Recovery in HRS-AKI

Restoring liver function by liver transplantation (LT) remains the only curative treatment for HRS-AKI [1, 8]. Pharmacological treatment with vasoconstrictors can potentially reverse the hemodynamic abnormalities associated with advanced cirrhosis, improve renal function, and extend short-term survival and can be a possible bridge to LT for patients with HRS-AKI [1, 2, 6, 9, 10]. Reversal of HRS or complete or full response has been the primary endpoint in clinical trials and pharmacological treatment goal of choice as outlined in ICA recommendations [5, 10]. A complete or full response to the pharmacologic treatment requires reduction of SCr to within 0.3 mg/dL of the baseline value measured within the previous 3 months of hospital admission or, if unavailable, the SCr value obtained upon hospital admission [5]. Since historical baseline SCr values are not always available, a full response may not be an achievable treatment goal for many patients. Previous studies have indicated that changes in SCr of > 10%–20% are clinically meaningful and within the range of serum changes regarded as significant in patients with AKI in general [11, 12]. Thus, the degree of improvement in SCr may be a more sensitive indicator of response to treatment than a defined target value of SCr [5].

1.3 | Terlipressin Treatment Response in HRS-AKI

Terlipressin, a vasopressin analogue, is the only pharmacological agent approved by the United States Food and Drug Administration for the treatment of adult patients with HRS-AKI [13]. Terlipressin plus albumin is recommended as the first-line treatment for patients with HRS-AKI, per the European Association for the Study of the Liver guidelines, and is the preferred vasoconstrictor therapy recommended by the American Association for the Study of Liver Diseases guidance [1, 8]. The safety and efficacy of terlipressin in patients with HRS-AKI have been demonstrated in three randomized, placebo-controlled Phase 3 studies (OT-0401, CONFIRM, and REVERSE) [14–16]. In all three studies, terlipressin demonstrated higher rates of HRS reversal compared to placebo; these results were statistically significant in two studies (OT-0401, 33.9% vs. 12.5%, respectively, $p = 0.008$; REVERSE, 23.7% vs. 15.2%, respectively; $p = 0.13$; CONFIRM, 39% vs. 18%, respectively; $p < 0.001$) [14–16]. In all studies, HRS reversal was defined as at least 1 SCr value of ≤ 1.5 mg/dL while on treatment, defined as up to 24 h after the final dose of terlipressin by Day 14 or discharge [14–16]. All three studies assessed improvement in renal function by additional prespecified endpoints such as change in SCr from start of treatment (SOT) to the end of treatment (EOT), and in CONFIRM, ≥ 30% SCr improvement was also analyzed as an exploratory prespecified endpoint. In the REVERSE study, a post hoc analysis demonstrated that even relatively small changes in SCr from baseline were associated with improved short-term survival, regardless of whether the patient achieved HRS reversal (defined as SCr ≤ 1.5 mg/dL) [5, 14]. The objective of this analysis is to evaluate the clinical outcomes of achieving > 30% improvement in SCr from SOT to EOT in a pooled population of patients with HRS-AKI treated with terlipressin.

2 | Methods

Data from OT-0401, REVERSE, and CONFIRM, three multicenter, randomized, double-blind, placebo-controlled Phase 3 studies, were pooled for this post hoc analysis [17]. The study designs, including eligibility criteria, and methods for each trial have been reported previously [14–16].

2.1 | Study Design

The CONFIRM, OT-0401, and REVERSE study populations consisted of adult patients with HRS-1 who were diagnosed using standard criteria before the adoption of the 2015 ICA HRS-AKI criteria [5]. Diagnosis of HRS-1 was per the clinical investigator and was defined as a rapidly progressive worsening in renal function with a doubling of SCr to ≥ 2.25 mg/dL in CONFIRM or ≥ 2.5 mg/dL in OT-0401 and REVERSE within 14 days before randomization [14–16]. Patients were excluded if they had sustained improvement in renal function (> 20% decrease in SCr in all three trials or SCr ≤ 2.25 mg/dL in CONFIRM) at least 48 h after diuretic withdrawal and plasma volume expansion with albumin [14–16]. Patients were treated with either terlipressin 1 mg or placebo via slow-push intravenous bolus over 2 min [14–16]. Concomitant administration of albumin (CONFIRM: 1 g/kg bodyweight to ≤ 100 g on Day 1 followed by 20–40 g/day; REVERSE: 20–40 g/day; OT-0401:100 g on Day 1 followed by 25 g/day) was recommended [14–16].

2.2 | Post Hoc Outcomes

Incidence of > 30% improvement in SCr from SOT to EOT was analyzed by treatment group across individual studies and pooled intent-to-treat (ITT) population. In most cases, the SOT

was defined as Day 0 of the study period, but a pre-study period value was used instead if the Day 0 value was missing. Change from SOT to EOT or Day 14 was defined as the EOT value minus the SOT value.

The pooled ITT population dataset was also evaluated by > 30% improvement in SCr from SOT to EOT for efficacy outcomes, including durability of HRS reversal (defined as the percentage of patients who had HRS reversal and no renal replacement therapy [RRT] to Day 30), incidence of RRT through Day 90, patients alive without RRT at Day 90, patients alive without transplant at Day 90, and overall survival through Day 90. Overall survival and RRT-free survival up to 90 days with and without HRS reversal and/or > 30% improvement in SCr SOT to EOT in the pooled ITT population was assessed using Kaplan–Meier estimates.

2.3 | Statistical Analyses

The ITT population, defined as all randomized patients, was used in the pooled analysis. Change from SOT through EOT in SCr was analyzed using repeated measure analysis of covariance (ANCOVA) based on a mixed-effect model. Baseline prognostic factors for > 30% improvement in SCr were evaluated by univariate and multivariate logistic regression analysis. In both the univariate and multivariate analyses, SCr concentrations were analyzed as a continuous variable.

The p values for continuous variables were calculated using the analysis of variance (ANOVA) and Kruskal–Wallis tests, whereas a Fisher exact test or χ^2 test was used for categorical variables.

2.4 | Safety

Safety assessments for incidence of serious adverse events (SAEs) reported in ≥ 5% of patients in the terlipressin treatment group were evaluated in the pooled safety population (i.e., all randomly assigned patients who received at least one dose of terlipressin; collated from the Phase 3 studies OT-0401, REVERSE, and CONFIRM) who achieved > 30% improvement in SCr from SOT to EOT [17].

3 | Results

3.1 | Incidence of > 30% Improvement in SCr From SOT to EOT

In the pooled ITT population ($N = 608$), 352 patients (CONFIRM, $n = 199$; REVERSE, $n = 97$; and OT-0401, $n = 56$) received terlipressin with a significantly higher proportion of patients compared with placebo achieving > 30% improvement in SCr from SOT to EOT (42.9% vs. 23.4%, respectively, $p < 0.001$) (Figure 1). Similarly, across all three studies, a significantly higher percentage of patients in the terlipressin group compared with placebo achieved > 30% improvement in SCr from SOT to EOT (37%–46% vs. 23%–24%, respectively; $p < 0.001$- $p = 0.03$) (Figure 1).

3.2 | Baseline Demographics and Clinical Characteristics

Baseline demographics were generally comparable between patients in the terlipressin group who achieved > 30% improvement in SCr from SOT to EOT and those who did not (Table 1). Statistically significant differences between the two subgroups were observed for the baseline model for end-stage liver disease (MELD) score (mean ± SD 31.3 ± 6.3 vs. 34.3 ± 6.2; $p < 0.001$), international normalized ratio (mean ± SD 2.1 ± 0.8 vs. 2.4 ± 0.8; $p < 0.001$), and baseline bilirubin (mean ± SD 10.4 ± 11.5 vs. 14.7 ± 13.3; $p < 0.001$) among others with slightly higher values noted for the ≤ 30% SCr improvement subgroup. Acute-on-chronic liver failure (ACLF) Grade 3 occurred in 27.9% of those who did not achieve > 30% improvement in SCr compared with 10.6% in those who achieved > 30% SCr improvement (Table 1). The most common etiology of cirrhosis

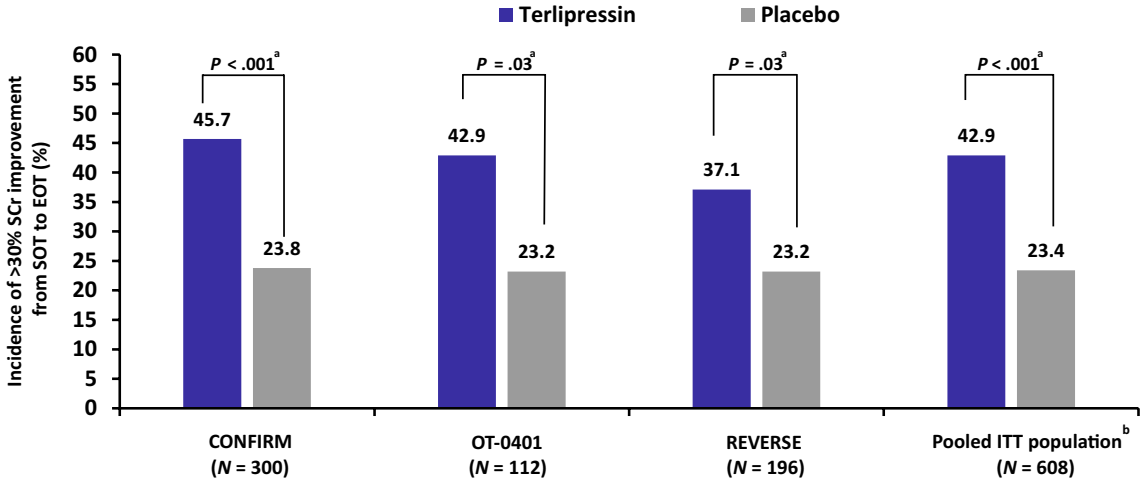

FIGURE 1 | Incidence of > 30% SCr improvement from SOT to EOT (individual studies and pooled ITT population). EOT, end of treatment; ITT, intent-to-treat; *N*, number of patients in the study and treatment group; SCr, serum creatinine; SOT, start of treatment. [a]*p* values from a χ^2 test. [b]Data pooled from the following Phase 3 studies: OT-0401, REVERSE, and CONFIRM.

TABLE 1 | Baseline demographics and clinical characteristics by at least 30% SCr improvement from SOT to EOT (terlipressin group, pooled ITT population).[a]

Parameters	Improvement in SCr from SOT to EOT		p[b]
	>30% improvement in SCr ($N=151$)	≤30% improvement in SCr ($N=201$)	
Age, years			0.92
Mean (SD)	54.2 (9.8)	53.9 (11.1)	
Minimum, maximum	23.3, 78.0	23.2, 77.0	
Sex, *n* (%)			0.10
Male	99 (65.6)	114 (56.7)	
Female	52 (34.4)	87 (43.3)	
Race, *n* (%)			0.75
White	137 (90.7)	176 (87.6)	
Asian	4 (2.6)	4 (2.0)	
Black or African American	8 (5.3)	16 (8.0)	
American Indian or Alaska Native	1 (0.7)	2 (1.0)	
Native Hawaiian or Pacific Islander	0 (0)	0 (0)	
Alcoholic hepatitis, *n* (%)	56 (37.1)	65 (32.3)	0.37
Alcoholic hepatitis, baseline MAP <70 mmHg, or SIRS, *n* (%)	103 (68.2)	130 (64.7)	0.50
Baseline SCr, mg/dL			<0.001
Mean (SD)	3.3 (0.8)	3.8 (1.5)	
Minimum, maximum	2.1, 6.4	1.7, 11.9	
Baseline MELD score			<0.001
n	131	181	
Mean (SD)	31.3 (6.3)	34.3 (6.2)	
Minimum, maximum	17.0, 40.0	16.0, 40.0	
Baseline Child-Pugh score			0.03
n	147	190	
Mean (SD)	10.1 (2.0)	10.6 (1.9)	
Minimum, maximum	6.0, 14.0	7.0, 15.0	
Baseline INR			<0.001
n	136	189	
Mean (SD)	2.1 (0.8)	2.4 (0.8)	
Minimum, maximum	1.0, 5.8	1.1, 5.2	
Baseline bilirubin, mg/dL			0.001
n	145	193	
Mean (SD)	10.4 (11.5)	14.7 (13.3)	
Minimum, maximum	0.4, 50.3	0.3, 51.6	

(Continues)

TABLE 1 | (Continued)

Parameters	Improvement in SCr from SOT to EOT		
	>30% improvement in SCr (*N*=151)	≤30% improvement in SCr (*N*=201)	*p*[b]
Baseline MAP, mm Hg			0.55
Mean (SD)	77.2 (11.3)	77.4 (12.5)	
Minimum, maximum	47.0, 112.7	48.0, 117.7	
Baseline ACLF grade, n (%)			<0.001
1	91 (60.3)	71 (35.3)	
2	44 (29.1)	72 (35.8)	
3	16 (10.6)	56 (27.9)	
Prior infection, *n* (%)	10 (6.6)	11 (5.5)	0.66
Etiology of cirrhosis, *n* (%)			
Alcohol	65 (43.0)	69 (34.3)	0.10
Nonalcoholic steatohepatitis	19 (12.6)	23 (11.4)	0.74
Hepatitis C	14 (9.3)	17 (8.5)	0.85
Autoimmune hepatitis	5 (3.3)	5 (2.5)	0.75
Primary biliary cirrhosis	2 (1.3)	3 (1.5)	>0.99
Hepatitis B	1 (0.7)	3 (1.5)	0.64
Prior albumin exposure, *n* (%)	143 (94.7)	187 (93.0)	0.66
Amount of prior albumin, g			0.08
n	134	178	
Mean (SD)	314.1 (196.4)	339.1 (180.7)	
Minimum, maximum	25.0, 1000.0	25.0, 925.0	

Abbreviations: ACLF, acute-on-chronic liver failure; EOT, end of treatment; INR, international normalized ratio; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, model for end-stage liver disease; *n*, number of patients for each baseline parameter; *N*, number of patients in the treatment group; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOT, start of treatment.
[a]Data pooled from the following phase 3 studies: OT-0401, REVERSE, and CONFIRM.
[b]For numeric data, ANOVA and Kruskal-Wallis tests were used to generate *p* values following testing for normality. For categorical data, Fisher exact test was used.

was alcohol-use in both subgroups (>30% SCr improvement, 43.0%; ≤30% SCr improvement, 34.3%), and alcoholic hepatitis was present at enrollment in 37.1% in the >30% SCr improvement subgroup versus 32.3% in the ≤30% SCr improvement subgroup. Prior albumin exposure and the mean amount of albumin exposure were not statistically significant between the two subgroups (Table 1).

3.3 | Predictors of >30% Improvement in SCr

Univariate logistic regression analysis identified several baseline characteristics that were associated with achieving >30% improvement in SCr from SOT to EOT in the pooled ITT population, including SCr (odds ratio, OR [95% confidence interval, CI: 0.66 (0.53–0.82)], $p<0.001$), MELD score (OR [95% CI: 0.93 (0.89–0.96)], $p<0.001$), Child-Pugh score (OR [95% CI: 0.87 (0.78–0.98)], $p=0.02$), and ACLF Grade 3 (OR [95% CI: 0.50 (0.37–0.67)], $p<0.001$) (Table 2). In the multivariate analysis, ACLF grade (OR [95% CI: 0.51 (0.38–0.69)], $p<0.001$), MELD score (OR [95% CI: 0.94 (0.90–0.97)], $p<0.001$), and baseline SCr (OR [95% CI: 0.66 (0.52–0.82)], $p<0.001$) remained predictors of achieving >30% improvement in SCr (Table 2).

3.4 | Durability of HRS Reversal

Durability of HRS reversal (defined as the percentage of patients with HRS reversal without RRT to Day 30) was achieved in significantly more patients in the terlipressin subgroup with >30% SCr improvement compared with the ≤30% SCr improvement subgroup (68.9% [95% CI: 0.6, 0.8] vs. 1.0% [95% CI: 0]) (Figure S1).

3.5 | Incidence of RRT Through Day 90

Among all patients who achieved >30% improvement in SCr compared with those who did not, the need for RRT was significantly lower through Day 30 (8.5% vs. 53.4%, respectively; $p<0.001$), Day 60 (11.9% vs. 54.8%, respectively; $p<0.001$), and Day 90 (14% vs. 55.2%, respectively; $p<0.001$) (Figure 2A).

TABLE 2 | Univariate and multivariate logistic regression of baseline characteristics by at least 30% SCr improvement from SOT to EOT (terlipressin group, pooled ITT population).[a]

Baseline parameters	*n*	Odds ratio	95% CI	*p*
Univariate logistic regression analysis				
Alcoholic hepatitis	352	1.23	0.79–1.92	0.35
Baseline SCr	352	0.66	0.53–0.82	< 0.001
Age < 65 years	352	1.11	0.62–2.00	0.73
Male sex	352	1.45	0.94–2.25	0.09
Baseline MELD score	312	0.93	0.89–0.96	< 0.001
Baseline Child-Pugh score	337	0.87	0.78–0.98	0.02
Baseline MAP	352	1.00	0.98–1.02	0.85
Baseline MAP < 65	352	0.54	0.28–1.04	0.06
Baseline ACLF grade	352	0.50	0.37–0.67	< 0.001
Multivariate logistic regression analysis				
Baseline SCr	352	0.66	0.52–0.82	< 0.001
Baseline MELD score	312	0.94	0.90–0.97	< 0.001
Baseline ACLF grade	352	0.51	0.38–0.69	< 0.001

Abbreviations: ACLF, acute-on-chronic liver failure; CI, confidence interval; EOT, end of treatment; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, model for end-stage liver disease; *n*, number of patients for each baseline parameter; SCr, serum creatinine; SOT, start of treatment.
[a]Data pooled from the following phase 3 studies: OT-0401, REVERSE, and CONFIRM.

3.6 | Patients Alive Without RRT at Day 90

Significantly more patients who achieved > 30% improvement in SCr were alive on Day 90 without the need for RRT compared with those who did not achieve 30% improvement in SCr, regardless of treatment (64.5% vs. 24.0%, respectively; $p < 0.001$) (Figure 2B). Similarly, when looking at only the terlipressin group, significantly more patients who achieved > 30% improvement in SCr were alive on Day 90 without the need for RRT compared with those who did not achieve 30% improvement in SCr (61.6% vs. 22.7%, respectively; $p < 0.001$).

3.7 | Patients Alive Without Transplant at Day 90

Significantly more patients who achieved > 30% improvement in SCr were alive on Day 90 without transplant compared with those who did not achieve 30% improvement in SCr, regardless of treatment (44.1% vs. 14.2%, respectively; $p < 0.001$) (Figure 2C). In the terlipressin group, significantly more patients who achieved > 30% improvement in SCr were alive on Day 90 without transplant compared with those who did not achieve 30% improvement in SCr (43.0% vs. 11.6%, respectively; $p < 0.001$).

3.8 | Overall Survival by Day 90

Significantly more patients who achieved > 30% improvement in SCr from SOT to EOT were alive by Day 90 than the ≤ 30% SCr improvement subgroup (71.1% vs. 41.6%, respectively; $p < 0.001$), regardless of treatment (Figure 3).

3.9 | Overall Survival by Day 90 for Patients With HRS Reversal and no HRS Reversal With or Without > 30% SCr Improvement

Patients without HRS reversal but who achieved > 30% improvement in SCr from SOT to EOT had higher overall survival by Day 90 compared with the subgroup who did not achieve > 30% improvement in SCr (Figure S2). Importantly, overall survival in the group achieving > 30% improvement in SCr from SOT to EOT without HRS reversal was comparable to the overall group who achieved HRS reversal (Figure S2).

3.10 | RRT-Free Survival by Day 90 for Patients With HRS Reversal and no HRS Reversal With or Without > 30% SCr Improvement

Patients without HRS reversal but who achieved > 30% improvement in SCr from SOT to EOT had higher RRT-free survival by Day 90 compared with the subgroup who did not achieve > 30% improvement in SCr (Figure 3). RRT-free survival in the group achieving > 30% improvement in SCr from SOT to EOT without HRS reversal was comparable to the overall group who achieved HRS reversal (Figure S3).

3.11 | Safety

The mean total exposure for terlipressin was statistically higher in those who achieved > 30% SCr improvement than those who did not (42.1 ± 30.8 mg vs. 14.7 ± 16.8 mg, respectively; $p < 0.001$). The mean ± SD duration of terlipressin exposure was

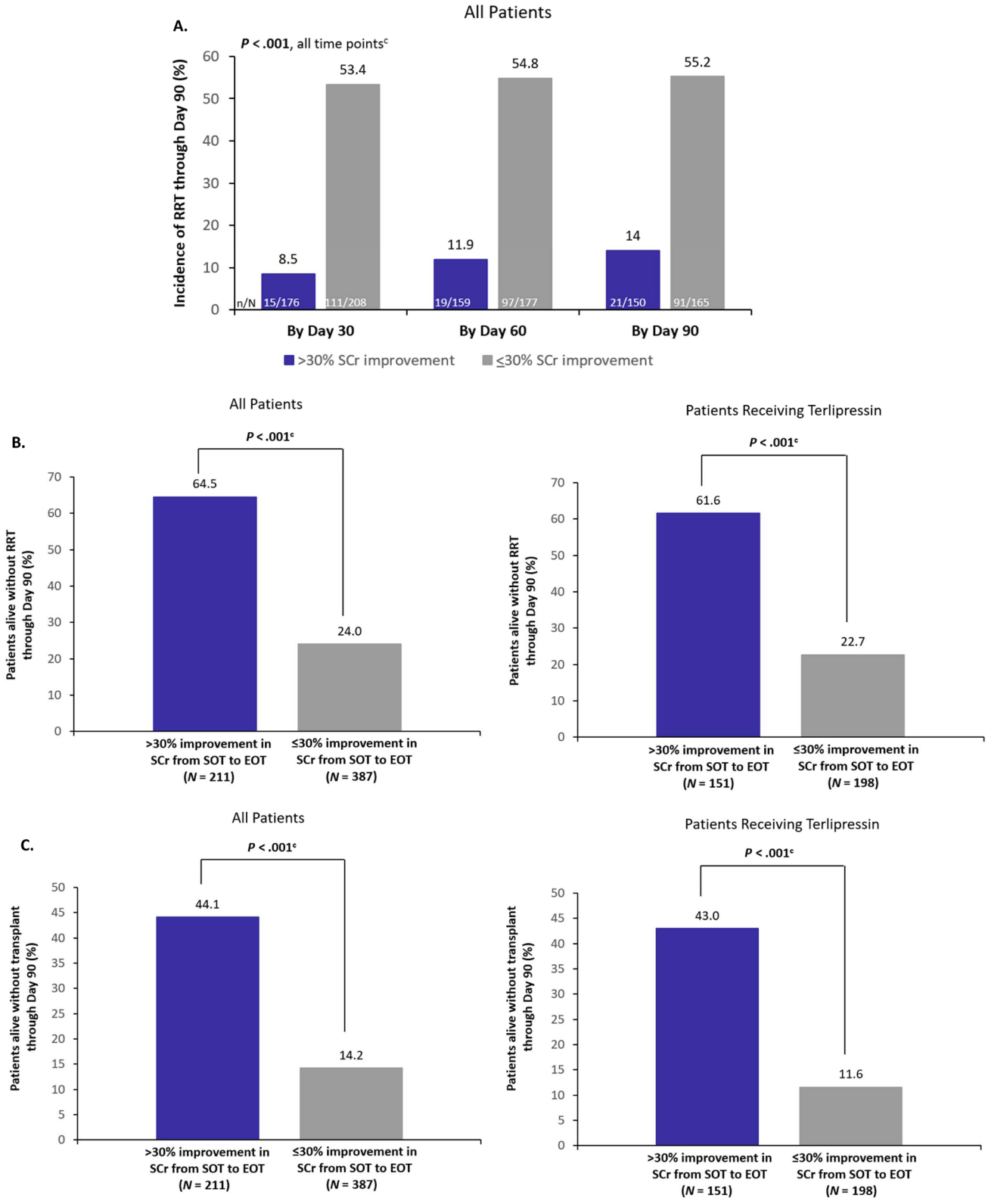

FIGURE 2 | Incidence of RRT through Day 90[a] (A), patients alive without RRT[b] (B), and patients alive without transplant[b] (C) by > 30% SCr Improvement From SOT to EOT (pooled ITT population). EOT, end of treatment; ITT, intent-to-treat; N, number of patients in the treatment group who are alive at the time point; n, number of patients in the category of patients alive at the time point in the treatment group; RRT, renal replacement therapy; SCr, serum creatinine; SOT, start of treatment. [a]Data pooled from the following phase 3 studies: OT-0401, REVERSE, and CONFIRM and includes both terlipressin and placebo groups. [b]Data pooled from the following phase 3 studies: OT-0401, REVERSE, and CONFIRM. [c]*p* values from a χ^2 test.

9.2 ± 4.5 days in the > 30% SCr improvement subgroup versus 4.0 ± 2.6 days in the ≤ 30% SCr improvement subgroup. While the majority of patients in both subgroups received the standard dose of terlipressin, a significantly higher proportion of patients who achieved > 30% SCr improvement received a high dose of terlipressin, defined as ≥ 1 dose of 2 mg, compared to those who did not achieve > 30% SCr improvement (37.7% vs. 19.2%, respectively; $p < 0.001$) (Table 3).

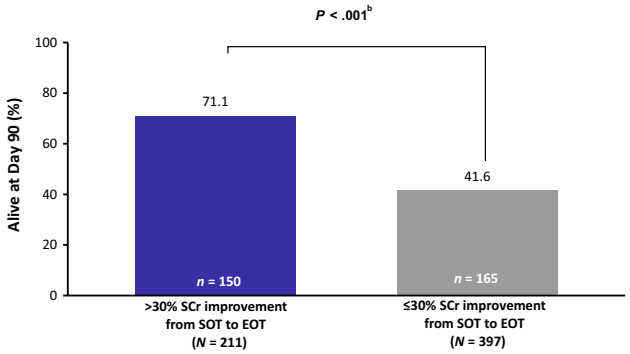

FIGURE 3 | Overall survival up to 90 days by > 30% SCr improvement from SOT to EOT (pooled ITT population).[a] EOT, end of treatment; ITT, intent-to-treat; N, number of patients in the treatment group who are alive at the time point; *n*, number of patients in the category of patients alive at the time point in the treatment group; SCr, serum creatinine; SOT, start of treatment. [a]Data pooled from the following Phase 3 studies: OT-0401, REVERSE, and CONFIRM and includes both terlipressin and placebo groups. [b]*p* value from a χ^2 test.

The overall percentage of patients with adverse events (AEs) was similar between the two subgroups. However, the overall incidence of SAEs was higher in those who did not achieve > 30% improvement in SCr (76.3%) compared with those who did (60.3%). Among the SAEs reported by ≥ 5% of patients within a treatment group, hepatobiliary, respiratory, thoracic, and mediastinal disorders, multiple organ dysfunction syndrome, and general disorders and administration-site conditions were reported significantly more frequently in those who did not achieve > 30% SCr improvement compared with those who did. No statistically significant changes were noted in the incidence of gastrointestinal disorders, infections, infestations, respiratory, and chronic hepatic failure between the two subgroups (Table 4).

4 | Discussion

Restoring renal function is one of the most important goals of treatment in patients with HRS-AKI [18]. The results presented in this large, pooled analysis of patients with HRS-AKI are consistent with previously published data on the efficacy of terlipressin in improving renal function [14–16]. In this post hoc analysis, terlipressin treatment led to approximately twice as many patients achieving > 30% improvement in SCr compared to placebo. Patients who achieved this > 30% SCr improvement had more favorable clinical

TABLE 3 | Summary of exposure to treatment and HRS reversal rate for patients with or without > 30% SCr improvement from SOT to EOT (terlipressin group, pooled safety population).[a]

Parameters	Improvement in SCr from SOT to EOT		p^b
	> 30% improvement in SCr (*N* = 151)	≤ 30% improvement in SCr (*N* = 198)	
Treatment duration, days			
Mean (SD)	9.2 (4.5)	4.0 (2.6)	< 0.001
Total exposure,[c] mg			< 0.001
Mean (SD)	42.1 (30.8)	14.7 (16.8)	
Minimum, maximum	3.0, 153.0	1.0, 100.0	
Daily exposure, mg/day			< 0.001
Mean (SD)	4.20 (1.4)	3.07 (1.2)	
Minimum, maximum	1.17, 7.21	0.75, 6.67	
Dose level,[d] *n* (%)			
High	57 (37.7)	38 (19.2)	< 0.001
Standard	94 (62.3)	160 (80.8)	< 0.001
Patients achieving HRS reversal,[e] *n* (%)	113 (74.8)	4 (2.0)	< 0.0001

Abbreviations: ANOVA, Analysis of Variance; EOT, end of treatment; HRS, hepatorenal syndrome; *n*, number of patients in the category in the treatment group; *N*, number of patients in the treatment group; SCr, serum creatinine; SD, standard deviation; SOT, start of treatment.
[a]Data pooled from the following phase 3 studies: OT-0401, REVERSE, and CONFIRM.
[b]For numeric data, ANOVA and Kruskal-Wallis tests were used to generate *p* values following testing for normality. For categorical data, Fisher exact test was used.
[c]Exposure data are combined from both periods for patients receiving initial and re-treatment periods.
[d]Patients in the standard-dose level received only 0.5- and 1-mg doses. Patients in the high-dose level received at least 1 dose of 2 mg.
[e]HRS reversal was defined as at least 1 SCr value of ≤ 1.5 mg/dL while on treatment, which is defined as up to 24 h after the final dose of terlipressin by Day 14 or discharge.

TABLE 4 | Summary of adverse events in patients with HRS-AKI by at least 30% SCr improvement from SOT to EOT (terlipressin group, pooled safety population).[a]

AEs	Improvement in SCr from SOT to EOT		p[b]
	>30% improvement in SCr ($N=151$), n (%)	≤30% improvement in SCr ($N=198$), n (%)	
Any AE	142 (94.0)	189 (95.5)	0.55
Permanent withdrawals due to AEs	11 (7.3)	35 (17.7)	0.004
SAEs reported by ≥5% of patients within a treatment group by system organ class/preferred term			
Any SAE	91 (60.3)	151 (76.3)	0.001
Gastrointestinal disorders	22 (14.6)	26 (13.1)	0.70
Abdominal pain	9 (6.0)	6 (3.0)	0.18
General disorders and administration-site conditions	8 (5.3)	25 (12.6)	0.02
Multiple organ dysfunction syndrome	5 (3.3)	23 (11.6)	0.005
Hepatobiliary disorders	27 (17.9)	60 (30.3)	0.008
Chronic hepatic failure	7 (4.6)	19 (9.6)	0.08
Hepatic failure	8 (5.3)	18 (9.1)	0.18
Infections and infestations	19 (12.6)	30 (15.2)	0.49
Sepsis	6 (4.0)	13 (6.6)	0.29
Respiratory, thoracic, and mediastinal disorders	18 (11.9)	41 (20.7)	0.03
Respiratory failure	9 (6.0)	21 (10.6)	0.13

Abbreviations: AE, adverse event; EOT, end of treatment; HRS-AKI, hepatorenal syndrome-acute kidney injury; n, number of patients for each baseline parameter; N, number of patients in the treatment group; SAE, serious adverse event; SCr, serum creatinine; SOT, start of treatment.
[a]Data pooled from the following phase 3 studies: OT-0401, REVERSE, and CONFIRM.
[b]If the number of events per cell <5, then a Fisher exact test was used. Otherwise, a chi-square test was used.

outcomes than those who did not reach the threshold. In the >30% SCr improvement subgroup, 70% of patients demonstrated durability of HRS reversal, shown by the absence of RRT for at least 30 days, compared to 1% of those who did not achieve the 30% SCr improvement. Patients with >30% improvement in SCr levels also had a significantly lower likelihood of requiring RRT by Day 90 and higher overall survival at Day 90 than those who did not achieve this response. Furthermore, the improvement in survival for patients achieving >30% improvement in SCr was comparable to those achieving HRS reversal. Thus, >30% improvement in SCr may indicate improved renal function and is a clinically meaningful endpoint. As expected, lower baseline SCr levels and ACLF grade were significantly associated by both univariate and multivariate analyses with achieving 30% improvement in SCr, thereby highlighting the need for early detection of HRS-AKI for better clinical outcomes.

4.1 | Implications for Clinical Practice

HRS reversal can lead to improved prognosis, including reduced intensive care unit length of stay and a reduced need for RRT before or after LT [18]. Using reduction in SCr levels at the time of presentation of HRS-AKI to EOT as a significant outcome may be more universally applicable than using a fixed 1.5 mg/dL cutoff. Understanding the definitions of these responses to treatment is crucial in managing patients, particularly those with cirrhosis, diabetes, and hypertension who develop HRS-AKI and may have chronic kidney disease (CKD) with SCr values >1.5 mg/dL (before developing HRS-AKI), thus making HRS reversal an unlikely outcome. In addition, with increasing incidence of nonalcoholic steatohepatitis and the presence of CKD, the prognostic and therapeutic implications of HRS-AKI have yet to be determined, and these implications will probably differ from those in patients with HRS-AKI that progresses to HRS-CKD [10, 19]. With increased understanding of the HRS-AKI pathophysiology, the traditional thinking of it as a functional failure needs to be reevaluated [8]. HRS-AKI may manifest as a spectrum that, if not diagnosed and treated early, can progress to significant injury [18]. Outcome measures that are sensitive to gauge treatment response to HRS-AKI are needed. As achieving >30% improvement in SCr levels from SOT to EOT was associated with clinically meaningful outcomes in this study, using such a threshold may be more universally applicable instead of an arbitrary reduction to 1.5 mg/dL to evaluate treatment response [6].

4.2 | Limitations of the Study

Study findings should be interpreted in the post hoc analysis study context. Prospective studies are needed to evaluate and

validate the clinical benefits of > 30% improvement in SCr levels in improving renal function in HRS-AKI.

5 | Conclusions

In patients with HRS-AKI receiving terlipressin, > 30% improvement in SCr may be a clinically meaningful endpoint even if they do not have a complete response or HRS reversal during treatment (as this accounts for patients with varying degrees of CKD at baseline). This new outcome measure is more aligned with the updated HRS-AKI definition of evaluating the improvement of renal function based on each patient's baseline SCr value rather than a reduction in SCr to a predefined level of < 1.5 mg/dL.

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Conflicts of Interest

M.A.M. reports participation in a Mallinckrodt Pharmaceuticals advisory board. M.K. has received grant funding not related to this project from CareDx Inc. and is an equity holder in R and R Medical LLC. K.J. is employed by Mallinckrodt Pharmaceuticals. The other authors declare no conflicts of interest.

Data Availability Statement

Discussion of statistical endpoints and analysis are included in the manuscript. Summary aggregate (basic) results (including adverse event information) and the study protocols will be available on clinicaltrials.gov (CONFIRM, NCT02770716; OT-0401, NCT00089570; REVERSE, NCT01143246) when required by regulation. Individual de-identified patient data will not be disclosed. Requests for additional information should be directed to the sponsor of the study at medinfo@mnk.com.

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Supporting Information

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