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ORIGINAL RESEARCH

Early Diagnosis and Timely Terlipressin in Hepatorenal Syndrome Improves Projected Outcomes and Lowers Cost

Juan F Gallegos-Orozco[1], Jacqueline G O'Leary[2], Kapuluru Gautham Reddy[3], Jas Bindra[4], Ishveen Chopra[5], John Niewoehner[6], Xingyue Huang[6]

[1]University of Utah, Salt Lake City, UT, USA; [2]University of Texas, Southwestern, Dallas, TX, USA; [3]University of Chicago Medicine, Chicago, IL, USA; [4]Falcon Research Group, North Potomac, MD, USA; [5]Manticore Consultancy, Bethesda, MD, USA; [6]Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA

Correspondence: Xingyue Huang, Mallinckrodt Pharmaceuticals, 440 US-22 Suite 302, Bridgewater, NJ, 08807, USA, Email xingyue.Huang@mnk.com

Introduction: Terlipressin is the only Food and Drug Administration-approved medication for adults with hepatorenal syndrome-acute kidney injury (HRS-AKI) with rapid reduction in kidney function. Treatment with terlipressin, particularly in patients with lower serum creatinine (SCr) at diagnosis, improves outcomes. Despite evidence suggesting that treating HRS-AKI at lower SCr thresholds may improve clinical outcomes, the impact on healthcare resource utilization (HCRU) and medical costs of an earlier intervention strategy remains unquantified. This model-based analysis was conducted from a United States hospital perspective to project the clinical and economic impact of early HRS-AKI diagnosis and treatment with terlipressin among adults.

Methods: A decision-analytic model compared two SCr level-based scenarios and projected the outcomes for both scenarios. For current clinical practice, patient distribution was based on the CONFIRM trial (SCr <3 mg/dL: 45% and ≥3 to <5 mg/dL: 55%). For early diagnosis and treatment, distribution was based on the HRS medical chart review study (<3 mg/dL: 85% and ≥3 to <5 mg/dL: 15%). Terlipressin HRS reversal rate for the on-label population (SCr <5 mg/dL and acute-on-chronic liver failure grade 0–2) was 52.2% for SCr <3 mg/dL and 33.3% for SCr ≥3 to <5 mg/dL. An annual HRS incidence of 50,000 was assumed.

Results: Based on the modeled projections, early diagnosis and treatment with terlipressin versus current practice yielded an additional 3040 HRS reversals and consequently led to a reduction in hospital days and intensive care unit days. Early intervention resulted in 960 fewer patients requiring renal replacement therapy during hospitalization and 1200 more patients with 90-day transplant-free survival. Early intervention is projected to save $11,504 per patient, with total national savings of $460.2 million annually.

Conclusion: Based on the modeled projections using data from clinical trial, earlier HRS diagnosis and treatment with terlipressin may improve clinical outcomes, reduce HCRU, and save costs versus current clinical practice.

Keywords: hepatorenal syndrome, early diagnosis, serum creatinine, HRS reversal, healthcare resource use

Introduction

Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a potentially reversible form of AKI that is a rare, life-threatening complication of cirrhosis.[1,2] HRS-AKI is characterized by rapidly progressive kidney failure in individuals with severe liver disease, often in the setting of advanced cirrhosis or acute-on-chronic liver failure (ACLF).[1,3–5] The pathophysiology of HRS involves intense splanchnic vasodilation, reduced effective arterial blood volume, and renal vasoconstriction, ultimately leading to decreased renal perfusion and kidney function.[2] The prognosis for HRS-AKI is poor without timely intervention, resulting in high mortality rates.[3,6–8] A recently published retrospective study reported an HRS in-hospital mortality rate of 34.2% among United States (US) adults.[9] Further, the median survival time is reported to be less than 2 weeks for untreated HRS-AKI, with 80% mortality within 3 months.[10] In addition, HRS-AKI results in a substantial economic burden, with an estimated annual direct medical cost of $3–3.8 billion to US payers.[11]

In clinical practice, HRS-AKI represents the final common pathway of severe portal hypertension and renal vasoconstriction, yet definitive treatment with liver transplantation remains underutilized due to organ scarcity, comorbid

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contraindications, and delayed referral. Early detection of HRS-AKI is integral to improving prognosis. Early identification and prompt treatment of HRS-AKI may lead to better clinical outcomes.[3,12] Given that rapidly deteriorating kidney function often leads to a need for renal replacement therapy (RRT) and liver transplantation,[12–14] optimal HRS-AKI management is crucial for restoring renal function, avoiding renal replacement therapy, or delaying liver transplantation. The shortage of organ donors can result in long waiting lists for transplants.[15] As a consequence, many patients receive only supportive care or vasoconstrictors late in their disease course, when renal injury is more advanced. Patients with HRS-AKI can die while waiting for a transplant due to a limited supply of donor organs.[16] Better renal function is also important for patients undergoing liver transplantation to improve post-transplant outcomes. Better pre-transplant renal function has been linked to lower rates of post-transplant liver dysfunction and improved 30-day survival.[17]

In addition, early intervention with terlipressin can prevent the progression to more severe stages of kidney failure, thereby reducing the need for intensive care unit (ICU) stays, RRT, and other costly interventions.[12] Analysis of three North American clinical trials[2,18,19] showed that patients with lower serum creatinine (SCr) levels experienced greater benefits from terlipressin at diagnosis, emphasizing the importance of early identification and treatment of HRS.[12] Terlipressin (TERLIVAZ®), a synthetic vasopressin analog, binds to vasopressin receptors and acts as a systemic vasoconstrictor. Thus, it counteracts the splanchnic arterial vasodilation associated with HRS-AKI and restores blood flow to the kidneys.[20] Currently, terlipressin is the only US Food and Drug Administration (FDA)-approved medication indicated to improve kidney function in adult patients with HRS-AKI.[21] Terlipressin plus albumin is recommended as the first-line treatment for HRS-AKI by the European Association for the Study of the Liver.[5] It is also the preferred vasoconstrictor therapy recommended by the American Association for the Study of Liver Diseases.[4] Instituting standardized hospital protocols—such as automated SCr monitoring with trigger thresholds, multidisciplinary rounds including transplant and nephrology teams, and pre-set terlipressin order sets—could both streamline early diagnosis and facilitate timely consideration of transplantation, thereby maximizing clinical benefit and resource efficiency.

Despite evidence suggesting that treating HRS-AKI at lower SCr thresholds may improve clinical outcomes, the impact on healthcare resource utilization (HCRU) and medical costs of an earlier intervention strategy remains unquantified. We therefore hypothesized that diagnosing HRS-AKI at SCr <3 mg/dL and initiating terlipressin sooner would (i) improve key clinical outcomes and (2) reduce both HCRU and associated medical costs compared with current practice. To test this, a model-based analysis was conducted from a US hospital perspective to evaluate the clinical and economic impact of early HRS-AKI diagnosis and treatment with terlipressin among adults.

Methods

Model Overview

A decision-analytic model was developed in Microsoft® Excel to evaluate the clinical outcomes and HCRU across two different scenarios based on the distribution of patients across SCr groups at the time of HRS-AKI diagnosis (Figure 1).[12] In the current clinical practice scenario, based on the analysis of CONFIRM trial data among patients with SCr <5 mg/dL, it was assumed that 45% had SCr <3 mg/dL and 55% had SCr ≥3 to <5 mg/dL.[19] In the early diagnosis and treatment scenario, patient distribution was assumed to be 85% with SCr <3 mg/dL and 15% with SCr ≥3 to <5 mg/dL, based on results from an HRS medical chart review study in the United Kingdom.[22]

Patient Population

The model only assessed terlipressin treatment in the on-label population, ie, among patients with SCr <5 mg/dL and ACLF grade 0–2.[21] Therefore, patients with SCr ≥5 mg/dL or grade 3 ACLF were excluded from the analysis. The annual incidence of HRS-AKI was estimated at 50,000 adults based on the Premier Healthcare Database.[7] It is estimated that 80% of the annual adult HRS-AKI patients (approximately 50,000) would meet the terlipressin label criteria, which include approximately 40,000 patients (with SCr <5 mg and ACLF ≤2) for the analysis.[7] The model assessed the short-term clinical outcomes and economic impact of early diagnosis and treatment.

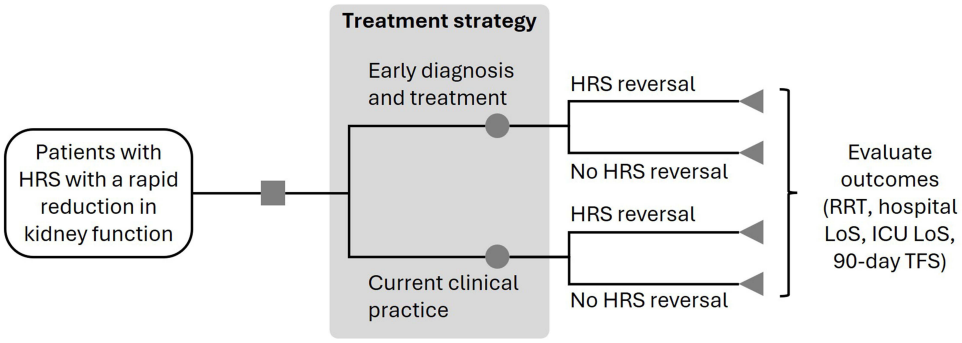

Figure 1 Schematic of the decision-analytic model.
Abbreviations: ICU, intensive care unit; HRS, hepatorenal syndrome; LoS, length of stay; RRT, renal replacement therapy; TFS, transplant-free survival.

Model Inputs

The model included HRS-AKI reversal (HRSR) rates, ICU and general ward length of stay (LoS), RRT rates during hospitalization, 90-day transplant-free survival (TFS), and costs associated with hospitalization (Table 1). HRSR was defined as at least 1 SCr value of ≤1.5 mg/dL while on treatment (on treatment was defined as up to 24 h after the final dose of terlipressin) by Day 14 or discharge.[12] The HRSR rate for terlipressin for the on-label population (SCr <5 mg/dL and ACLF grade 0 to 2) was derived from published clinical trials; higher reversal rates were observed in patients with lower baseline SCr levels.[12] Curry et al conducted a post hoc pooled analysis of 3 North American-centric, Phase 3, placebo-controlled clinical studies (OT-0401, REVERSE, and CONFIRM) across 3 SCr subgroups (ie <3, ≥3–<5, and ≥5 mg/dL) in patients with cirrhosis, ascites, and HRS-AKI who were treated with terlipressin or matched placebo.[12]

The RRT rate for patients by treatment response (HRSR or no HRSR) was estimated based on pooled data from 3 randomized clinical trials (CONFIRM, REVERSE, and OT0401).[2,18,19] Similarly, the proportion of patients with 90-day TFS rates was estimated based on pooled data from 3 randomized clinical trials (CONFIRM, REVERSE, and OT0401).[2,18,19]

The overall hospital LoS by SCr level was only considered for the patients with SCr <5 and ACLF grade 0–2 and derived from the CONFIRM trial and consistent with terlipressin label.[19] The proportion of patients treated in the ICU

Table 1 Key Inputs for Analysis

Clinical Parameter	**Patients with SCr <3 mg/dL**	**Patients with SCr ≥3-<5 mg/dL**	**Sources**
HRS reversal rate	52.2%	33.3%	Curry et al (2023)[12]
Average LoS[a]	23.4 days	29.2 days	Curry et al (2023)[12]
Healthcare resource use	**Patients with HRS reversal**	**Patients with no HRS reversal**	
RRT rate	11.3%	42.5%	Pooled analysis of three RCTs (OT-0401,[18] REVERSE,[2] and CONFIRM[19])
90-day survival without transplant	63.1%	23.6%	Pooled analysis of three RCTs (OT-0401,[18] REVERSE,[2] and CONFIRM[19])
Percent patients in ICU	9%	18%	Huang et al (2023)[23]
Average ICU LoS	6.0 days	9.1 days	Huang et al (2023)[23]
Costs	**General floor**	**ICU**	
Cost per hospital day	$4561	$6731	Abstract 178 (JHP 2014);[6] Rice et al (2017)[11]

Note: [a] Patients with SCr <5 mg/dL and acute-on-chronic liver failure range of 0–2 were only considered.
Abbreviations: HRS, hepatorenal syndrome; ICU, intensive care unit; LoS, length of stay; RCT, randomized controlled trial; RRT, renal replacement therapy; SCr, serum creatinine.

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and duration of ICU LoS by treatment response/HRSR was derived from the CONFIRM trial.[19] The daily costs for the general floor and ICU were sourced from the published literature.[6,11]

Model Outcomes

The model outcomes comparing early HRS-AKI diagnosis and treatment with terlipressin scenario versus current clinical practice scenario comprised clinical outcomes, HCRU, and hospitalization-related cost savings. Outcomes for each scenario were calculated separately. Costs were considered from a US hospital perspective. Costs were inflated to 2023 US Dollars utilizing the historical Consumer Price Index for medical care from the US Bureau of Labor Statistics.[24] Details for the calculation of model outcomes are provided as follows.

Clinical Outcomes

Overall HRSR Rate with Terlipressin

$(HRSR_{SCr<3\ mg/dL} \times \text{Proportion of patients}_{SCr<3\ mg/dL}) + (HRSR_{SCr\geq3-<5\ mg/dL} \times \text{Proportion of patients}_{SCr\geq3-<5\ mg/dL})$

Day-90 Survival without Transplant Rate

$(\text{Overall HRSR rate} \times \text{Day-90 TFS rate}_{HRSR}) + ([1 - \text{Overall HRSR rate}] \times \text{Day-90 TFS rate}_{No\ HRSR})$

Healthcare Resource Utilization

RRT Rate During Hospitalization

$(\text{Overall HRSR rate} \times \text{RRT rate}_{HRSR}) + ([1 - \text{Overall HRSR rate}] \times \text{RRT rate}_{No\ HRSR})$

Average Hospital LoS

$(\text{HRSR rate}_{Scr<3\ mg/dL} \times \text{Average LoS}_{Scr<3\ mg/dL}) + (\text{HRSR rate}_{Scr\geq3-<5\ mg/dL} \times \text{Average LoS}_{Scr\geq3-<5\ mg/dL})$

Average ICU Days

$(\text{Overall HRSR rate} \times \text{Average number of patients in ICU}_{HRSR} \times \text{Average LoS days}_{HRSR}) + ([1 - \text{Overall HRSR rate}] \times \text{Average number of patients in ICU}_{No\ HRSR} \times \text{Average LoS days}_{No\ HRSR})$

Hospitalization-Related Cost Savings

$(\text{Average ICU days} \times \text{Cost per ICU day}) + ([\text{Average LoS}_{General\ floor} - \text{Average ICU days}] \times \text{Cost per day}_{General\ floor})$

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses were employed to evaluate the baseline assumptions and assess the influence of variations in model parameters on the robustness of the difference in scenarios across all outcomes. A one-way deterministic sensitivity analysis was performed by altering each key model input by ±25%. A multivariable probabilistic sensitivity analysis was conducted using 10,000 Monte Carlo simulations, where parameter values were randomly sampled from predefined probability distributions, allowing for a comprehensive evaluation of combined uncertainty. The selection of these distributions was informed by the inherent characteristics and limitations of the available data.

Results

Base Case Analyses

Early diagnosis and treatment of HRS-AKI with terlipressin showed improved clinical outcomes and reduced HCRU compared to current clinical practice (Figure 2).

Increased HRS-AKI Response Rates

Early diagnosis and treatment strategy resulted in a numerically higher number of HRSRs (49.4% vs 41.8%), yielding an additional 3040 HRSRs compared to current clinical practice. This improvement may have implications for patient outcomes and resource allocation in US hospitals, where timely intervention is crucial for managing HRS-AKI in high-risk populations.

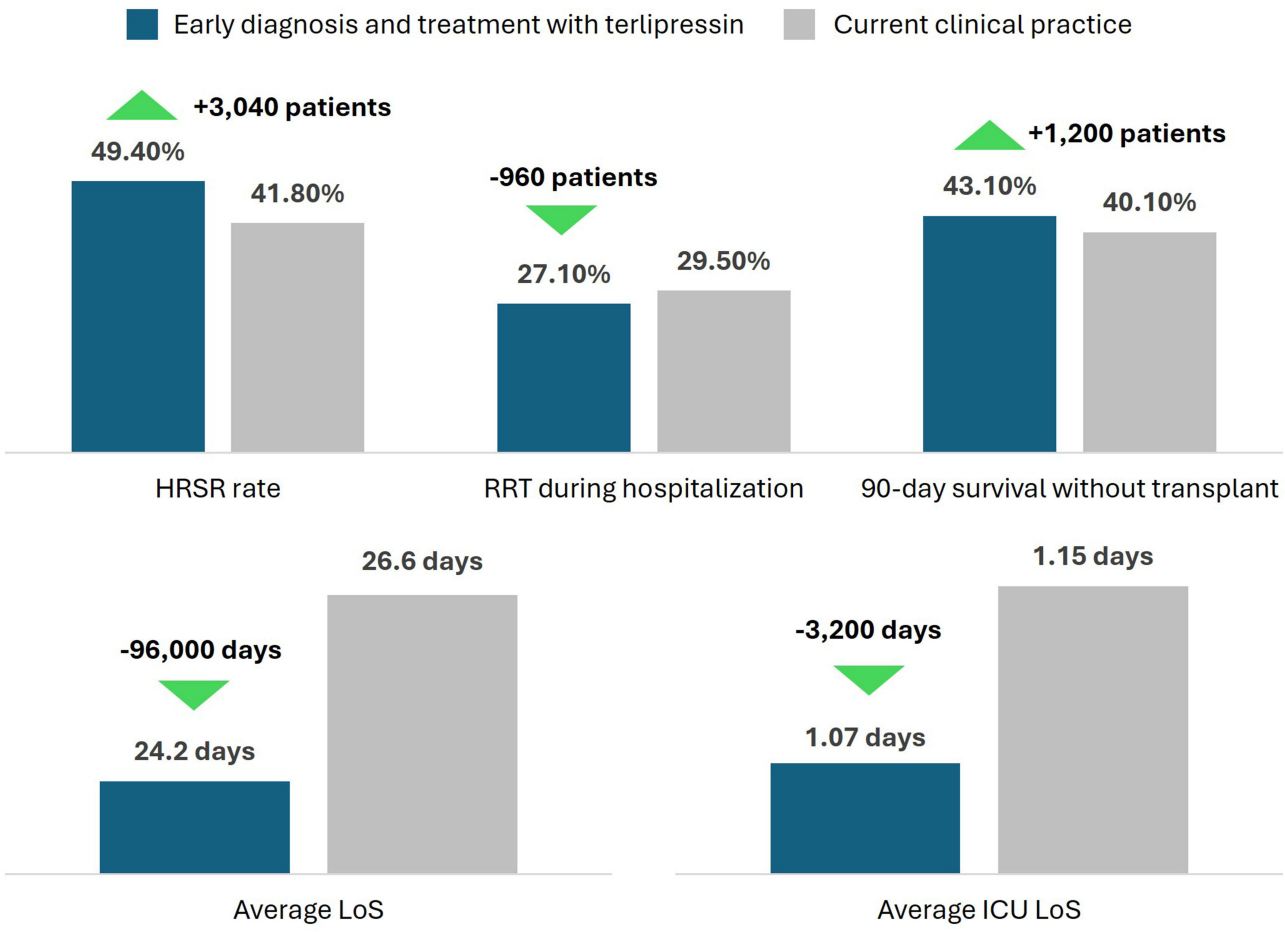

Figure 2 Incremental benefit with early diagnosis and treatment with terlipressin.
Notes: (i) The analysis assumes 80% of patients meet terlipressin label criteria out of the annual incidence of 50,000 adults (based on the Premier Healthcare Database) with hepatorenal syndrome in the United States. The incremental benefit is calculated by multiplying the difference between the scenarios by 40,000 patients (80% of 50,000).[7] (ii) Bolded values are the absolute differences between the early diagnosis and treatment with terlipressin scenario versus current clinical practice, projected over a modeled cohort of 40,000 patients. For the clinical outcomes (HRSR rate, RRT during hospitalization, 90-day survival without transplant), the difference in percentage points was multiplied by 40,000 to yield the difference in patient count. For the LoS outcomes (average LoS, average ICU LoS), the difference in days was multiplied by 40,000 to yield total days saved. Arrows denote the direction of projected difference (↑ increase; ↓ decrease) for the early diagnosis and treatment with the terlipressin scenario versus the current clinical practice scenario.
Abbreviations: HRSR, hepatorenal syndrome reversal; ICU, intensive care unit; LoS, length of stay; RRT, renal replacement therapy.

Reduced Hospital and ICU Stays

Consequently, patients who underwent early diagnosis and treatment experienced a numerically shorter duration of hospital stay (24.2 vs 26.6 days) and ICU stay (1.07 vs 1.15 days), translating to a total reduction of 96,000 hospital days and 3200 ICU days, respectively. This reduction may ease the burden on hospital resources, potentially lowering healthcare costs and improving bed availability, which is particularly vital during periods of high patient influx, such as flu season or pandemics.

Decreased Need for Dialysis

Numerically, fewer patients with early diagnosis and treatment strategy required RRT (27.1% vs 29.5%), with a reduction of 960 patients needing dialysis. This decrease in dialysis may enhance patient quality of life and reduce the strain on dialysis centers and hospital dialysis units, thereby optimizing the allocation of these specialized, limited resources.

Favorable 90-Day Transplant-Free Survival

A numerically higher proportion of patients with the early intervention strategy survived 90 days without requiring a liver transplant (43.1% vs 40.1%), resulting in 1200 more patients achieving this outcome. This improvement highlights the

potential effectiveness of the early intervention strategy in prolonging survival and reducing the need for expensive and complex transplant procedures, thus benefiting both patients and the broader healthcare system.

These improvements in patient outcomes translated into projected cost savings. Reduced hospitalization and ICU stays contributed to cost savings of $11,504 per person. On a national level, early diagnosis and treatment of HRS-AKI with terlipressin were estimated to save $460.2 million annually in the US. The national savings estimate ($460 million) is illustrative and assumes full protocol adoption; real-world uptake, pilot study results, and implementation costs are needed to refine these projections.

Sensitivity Analyses

The deterministic sensitivity analysis showed that early diagnosis of HRS and treatment with the terlipressin strategy may result in improved clinical outcomes and may potentially reduce resource utilization and healthcare costs compared to the current treatment strategy (Table 2). When key inputs were varied by ±25%, early intervention yielded between 920 and 5120 additional patients achieving HRSR, 280 to 1600 fewer requiring renal replacement therapy, and 360 to 2040 more patients surviving 90 days without transplant. Resource use was similarly lower, reductions of 1040 to 5600 ICU days and up to 212,000 aggregate hospital days were observed, depending on the parameter varied. Hospitalization cost savings per patient ranged from approximately $180 to $24,353.

Table 2 Deterministic Sensitivity Analysis Comparing Early Diagnosis of HRS and Treatment with Terlipressin and the Current Treatment Strategy

Parameter	Lower Bound	Upper Bound
Number of patients with HRSR		
SCr at diagnosis/Treatment initiation (<3 mg/dL)	920	5120
SCr at diagnosis/Treatment initiation (≥3–<5 mg/dL)	4360	1680
Number of patients with RRT during hospitalization		
SCr at diagnosis/Treatment initiation (<3 mg/dL)	−280	−1600
SCr at diagnosis/Treatment initiation (≥3–<5 mg/dL)	−1360	−520
RRT rate (HRSR)	−1040	−840
RRT rate (NHRSR)	−640	−1280
Number of patients with 90-day survival without transplant		
SCr at diagnosis/Treatment initiation (<3 mg/dL)	360	2040
SCr at diagnosis/Treatment initiation (≥3–<5 mg/dL)	1720	680
Transplant-free days rate (HRSR)	720	1680
Transplant-free days rate (NHRSR)	1360	1040
Average LoS days		
Hospital LoS (<3 mg/dL)	−188,000	0
Hospital LoS (≥3–<5 mg/dL)	20,000	−212,000
Average ICU LoS days		
SCr at diagnosis/Treatment initiation (<3 mg/dL)	−1040	−5600
SCr at diagnosis/Treatment initiation (≥3–<5 mg/dL)	−4800	−1840
Patients in ICU (HRSR)	−3720	−2920
Patients in ICU (NHRSR)	−2080	−4560
ICU LoS (HRSR)	−3720	−2920
ICU LoS (NHRSR)	−2080	−4560

(*Continued*)

Table 2 (Continued).

Parameter	Lower Bound	Upper Bound
Hospitalization cost savings (per-patient)		
SCr at diagnosis/Treatment initiation (<3 mg/dL)	$11,002	$11,251
SCr at diagnosis/Treatment initiation (≥3–<5 mg/dL)	$11,206	$11,047
Hospital LoS (<3 mg/dL)	$21,617	$180
Hospital LoS (≥3–<5 mg/dL)	$2100	$24,353
Patients in ICU (HRSR)	$11,149	$11,104
Patients in ICU (NHRSR)	$11,059	$11,194
ICU LoS (HRSR)	$11,149	$11,104
ICU LoS (NHRSR)	$11,059	$11,194
ICU cost per day	$10,987	$11,266
General floor cost per day	$8485	$13,768

Abbreviations: HRS, hepatorenal syndrome; HRSR, HRS reversal; ICU, intensive care unit; LoS, length of stay; NHRSR, no HRS reversal; RRT, renal replacement therapy; SCr, serum creatinine.

Table 3 Probabilistic Sensitivity Analysis Comparing Outcomes with Early Diagnosis of HRS and Treatment with Terlipressin and the Current Treatment Strategy

Outcome	Mean Difference (95% CI)
Number of patients with HRSR	2894 (2836, 2952)
Number of patients with RRT during hospitalization	−908 (−929, −887)
Number of patients with 90-day survival without transplant	1136 (1108, 1164)
Average LoS days	−3200 (−3289, −3111)
Average ICU LoS days	−93,713 (−97,235, −90,191)
Hospitalization cost savings (per patient)	$10,870 ($10,449, $11,292)

Abbreviations: CI, confidence interval; HRS, hepatorenal syndrome; HRSR, HRS reversal; ICU, intensive care unit; LoS, length of stay; RRT, renal replacement therapy.

The findings from the probabilistic sensitivity analysis were also consistent with the base case results (Table 3). Across 10,000 Monte Carlo simulations drawing all model inputs simultaneously, early diagnosis and treatment with terlipressin resulted in a mean of 2894 (95% confidence interval [CI]: 2836, 2952) additional HRSRs. Early diagnosis and treatment with the terlipressin strategy also resulted in fewer RRT events and more 90-day transplant-free survivors, reduced hospital and ICU LoS, with a mean per-patient cost savings of $10,870 (95% CI: $10,449, $11,292).

Discussion

HRS-AKI is a life-threatening condition; delayed diagnosis and treatment can lead to rapid deterioration of renal function and increased mortality.[1,2,9,10] To the best of our knowledge, this is the first study to assess the impact of early HRS diagnosis and treatment with terlipressin on HCRU and hospitalization-related costs versus current clinical practice from a US hospital perspective. Doing so can improve patient prognosis, reduce healthcare resource burden, and ultimately deliver more cost-effective care, particularly when resource optimization is critical. These findings emphasize the importance of integrating early diagnosis protocols and timely initiation of terlipressin into the standard care of HRS patients. The findings from this study demonstrated that early HRS diagnosis and terlipressin treatment yield greater HRSRs than current clinical practice. This strategy may also lead to fewer ICU days and a shorter overall hospital LoS, resulting in cost savings. In addition, the HRS diagnosis and treatment with terlipressin may result in a lower RRT rate during hospitalization and a higher 90-day survival without transplant. Overall, the analysis suggests that early diagnosis and treatment of HRS with terlipressin can be clinically beneficial and economically advantageous that may result in substantial savings for the healthcare system.

This analysis has important implications for clinical practice and healthcare management of patients with HRS. First, HRS may be reversible in its early stages with appropriate therapy. Early intervention provides an opportunity to restore kidney function[12–14] and decrease the likelihood of requiring liver transplantation or prolonged ICU stay.[12] Second, timely diagnosis and treatment can significantly improve patient outcomes. The results of this analysis align with previous research demonstrating that early intervention in HRS leads to better patient outcomes.[12,14] These findings, therefore, highlight the importance of implementing early detection strategies as a standard part of HRS management. Early intervention with terlipressin, especially in patients with lower SCr levels, is crucial for achieving favorable clinical outcomes. Patients treated earlier are more likely to experience HRSR, which may prevent progression to more severe kidney dysfunction. Timely diagnosis and treatment can also significantly improve patient outcomes through downstream benefits, such as reducing complications associated with renal failure, including fluid overload, electrolyte imbalances, and infections.[4,5] Third, early intervention can help maintain or improve a patient's quality of life by preserving kidney function, reducing the need for RRT, and preventing hospitalizations.[25–27] Fourth, early identification and treatment can prevent the progression of HRS to more advanced stages, which are often more challenging to manage and have a worse prognosis.[3,6–8,10] Fifth, addressing HRS promptly can help maintain eligibility for transplantation among patients who are candidates for liver transplantation and improve their chances of a successful outcome.[10,28] Sixth, early intervention reduces the need for costly and intensive treatments, including RRT and kidney transplantation, by improving kidney function before it further deteriorates.[29,30] Lastly, specific medications, such as terlipressin, are more effective when administered early in HRS,[12] emphasizing the importance of early diagnosis.

The current study also demonstrates the potential for substantial hospitalization-related healthcare cost savings, primarily by reducing ICU days and overall hospital LoS. Reducing HCRU alleviates the burden on already strained healthcare facilities, allowing for more efficient allocation of ICU beds and other critical resources.[7,11] In healthcare systems that are frequently operating at capacity, such reductions can improve care availability for other critically ill patients, emphasizing the broader systemic benefits of early intervention in HRS management.[7]

Although economic analyses specific to early HRS-AKI intervention are novel, our results are consistent with broader evidence that earlier intervention in acute conditions can yield net clinical and economic benefits. For example, a systematic review of health-economic evaluations in sepsis found that early goal-directed therapy often dominated usual care (ie, lower costs and better outcomes) in cost-effectiveness analyses.[31] In chronic inflammatory disease, an economic evaluation of early tumor necrosis factor inhibitor initiation in rheumatoid arthritis showed that starting therapy at 6 months (versus standard 12 months) produced an incremental cost-effectiveness ratio of £713–£17,335 per quality-adjusted life years gained, reflecting both improved utility and acceptable incremental costs.[32] These parallels support the general principle that timely diagnosis and treatment in high-risk populations can lead to both clinical and resource-use advantages, thereby bolstering the plausibility of our modeled projections in HRS-AKI.

Limitations

This analysis has several limitations. These projected outcomes rely on efficacy and cost inputs from published trials and US hospital sources; therefore, real-world patient heterogeneity and institutional cost variation may influence their applicability. The projected benefits should be interpreted in light of these structural and data constraints. First, efficacy inputs were drawn from controlled clinical trials and may not fully capture adherence patterns, comorbidities, or practice variations seen in routine care. Although external validation against real-world HRS-AKI cohorts would strengthen confidence in our projections, no existing datasets capture the required granularity in early diagnosis and resource use. Future work should prioritize the linkage of electronic health records or registry data to enable the calibration and validation of empirical models. Further, in this analysis, the distribution of patients in current clinical practice was based on the CONFIRM trial, in which about 60% of patients in both the terlipressin and placebo arms had received off-label midodrine plus octreotide prior to their first dose of study drug. Before the FDA approval of terlipressin, off-label vasoconstrictor regimens (midodrine and octreotide plus albumin in non-ICU settings and norepinephrine plus albumin in the ICU) constituted the standard of care. This background therapy may have influenced baseline renal responsiveness, potentially attenuating the incremental benefits observed with terlipressin. Second, cost inputs (eg, hospitalization, ICU, RRT) were based on average US hospital charges and may differ across regions or payer mixes. While costs were

inflation-adjusted and tested across plausible ranges, we did not model dynamic pricing shifts (eg, pandemic-related ICU cost surges), which could affect absolute savings estimates. Future research should incorporate time-series cost data to capture such volatility. Third, adverse events (AEs) associated with terlipressin (eg, respiratory failure) were not modeled, as both early- and later-diagnosis strategies assume identical terlipressin exposure and no evidence supports timing-dependent AE rates. Future analyses could incorporate aggregate AE costs and disutilities if comparative safety data by timing become available. Fourth, the modeled cohort (SCr < 3 mg/dL) may not reflect the timing of HRS-AKI recognition in all settings, and real-world delays in diagnosis could attenuate the projected benefits. Fifth, as per the current label for clinical use, patients with SCr ≥5 mg/dL or ACLF grade 3 were excluded from the present analysis. This is a limitation, though early diagnosis and treatment could reduce these cases. Lastly, the analysis is restricted to short-term outcomes (up to 90 days) due to the paucity of high-quality long-term data on HRS recurrence, chronic dialysis dependence, and post-transplant survival and costs. Consequently, mid- and long-term economic and clinical impacts were not projected, which may limit the generalizability of our findings beyond the immediate post-treatment period. Future observational or registry-based studies are needed to validate our projections and assess implementation barriers in diverse clinical environments.

Implementation and Future Directions

To translate these modeled projections into routine care, future work should focus on implementation research and real-world validation:

- Standardized Recognition Protocols. Many institutions currently lack formal HRS-AKI screening pathways. Pilot studies could evaluate the development and rollout of automated SCr alerts, structured order sets, and early nephrology/hepatology consultation triggers to assess feasibility, uptake, and impact on time-to-diagnosis and resource use.
- Liver Transplantation Considerations. Definitive management of HRS-AKI often involves liver transplantation, yet referral and listing rates remain suboptimal. Future analyses should capture the proportion of modeled patients, stratified by ascites severity and history of spontaneous bacterial peritonitis, who proceed to transplant listing or receipt, and quantify how earlier diagnosis may influence transplant timing, eligibility, and downstream costs.
- Real-World Data Integration. Linking electronic health record or registry data will enable Kaplan-Meier time-to-event modeling of survival benefits, subgroup analyses by cirrhosis etiology, and calibration of resource-use inputs across diverse hospital settings.
- Extended Outcomes and Perspectives. Subsequent models should extend the horizon beyond 90 days to include readmissions, post-transplant survival, and long-term dialysis costs, and consider payer and societal perspectives to fully characterize economic and quality-of-life impacts.

For model refinement, future analyses could (i) incorporate real-world data from electronic health records or registries to recalibrate efficacy and resource-use inputs; (ii) extend the time horizon beyond 90 days to capture long-term outcomes (eg, transplant rates, post-discharge costs); (iii) model AEs and off-protocol treatments, as well as drug acquisition costs, to provide a comprehensive budget-impact assessment; and (iv) explore a societal perspective and capture quality-adjusted life-years, enabling comparison with other health economic benchmarks. These steps will both facilitate clinical adoption and enhance the robustness and generalizability of future economic evaluations in HRS-AKI.

Conclusions

Modeled projections suggest that diagnosing HRS-AKI at a SCr threshold of <3 mg/dL and initiating terlipressin sooner may lead to improved rates of HRS reversal, fewer RRT events, shorter hospital and ICU stays, and lower overall resource use compared with current practice. Further, the findings suggested projected healthcare cost savings of $11,504 per person with early intervention compared to the current clinical practice. These findings, while based on a decision-analytic model rather than real-world data, highlight the potential economic and clinical value of earlier intervention. Prospective observational studies or registry analyses are needed to confirm these benefits in routine clinical settings.

We therefore advocate for the adoption of standardized HRS-AKI screening and early-treatment protocols that integrate automated SCr alerts and multidisciplinary consultation to drive institutional change and improve patient outcomes. Future work should also examine the long-term benefits, including the mitigation of chronic kidney disease progression post-HRS, and address the ethical and operational barriers to early diagnosis in resource-limited settings.

Abbreviations

ACLF, acute-on-chronic liver failure; AE, adverse event; AKI, acute kidney injury; CI, confidence interval; FDA, Food and Drug Administration; HCRU, healthcare resource utilization; HRS, hepatorenal syndrome; HRSR, hepatorenal syndrome reversal; ICU, intensive care unit; mg/dL, milligrams per deciliter; LoS, length of stay; RRT, renal replacement therapy; SCr, serum creatinine; TFS, transplant-free survival; US, United States.

Author Contributions

All authors made a significant contribution to the work reported, including study conception, design, execution, acquisition of data, analysis, and interpretation, and in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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