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Research Article

Albumin and Total Bilirubin on Admission and Peak Creatinine Predict Response to Treatment of Hepatorenal Syndrome-Acute Kidney Injury

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Abstract

Background: Hepatorenal syndrome-AKI (HRS-AKI) is a manifestation of decompensated cirrhosis and is characterized by rapid onset of renal failure with doubling of serum creatinine (Cr) to > 2.5 within a two-week period. Prognosis is poor with only 10% of patients surviving longer than 90 days. Due to limited availability and only recent FDA approval of Terlipressn in the USA, HRS has been mainly treated with albumin, midodrine, and octreotide. Data on response to therapy has remained mixed, with few studies on predictors of response. The aim of this study was to assess the role of total bilirubin, albumin, and international normalized ratio (INR) as predictors for response to treatment in HRS-AKI.

Methods: We performed a retrospective chart review on 371 adults with ICD-9/10 codes for decompensated cirrhosis and acute kidney injury. Patients were determined to have Type 1 vs 2 HRS as per the International Club of Ascites (ICA) guidelines. Patients had to meet the following criteria: cirrhosis with ascites, an acute increase in Cr to greater than 2.5 µmol/L within a two-week span, absence of shock defined as systolic blood pressure (SBP) < 90, no recent exposure to nephrotoxic agents, the absence of proteinuria (>500 g/dl) or pre-existing parenchymal disease, and no improvement in creatinine after discontinuation of diuretics and starting volume expansion. Other exclusion criteria included cardiac/respiratory failure, or prior beta-blocker use for variceal bleeding. All patients were treated with a combination of albumin, midodrine, and octreotide. Response to treatment was defined as the following within 3 days of initiation: Complete response – decrease in Cr to < 1.5 µmol/L, partial response – decrease in Cr by > 50% from baseline but not to < 1.5 µmol/L, no response – no decrease in Cr. Total bilirubin, albumin, and INR at admission and peak creatinine were compared among the different responder groups. Two-tailed T-testing was used for statistical analysis.

Results: Out of a total of 78 patients included, 23 (29.49%) achieved a complete response, 8 (10.26%) had partial response, 47 (60.26%) had no response. The mean total bilirubin (mg/dL) in the respective groups were 6.27±4.72, 9.76±8.47 and 10.94 ±11.78. The mean albumin (g/dL) in each respective group was 3.04±0.60, 2.74±0.66 and 2.71±0.50. Mean INRs were 1.90±0.91, 1.81±0.40, and 1.91±0.88. Mean Peak creatinine 3.17±1.72, 3.24±0.84, and 4.05±1.61. When compared to the no response group, the complete response group had a significant difference with a lower total bilirubin (P=0.02), higher albumin (P=0.03), and lower peak creatinine (P=0.04). There was no significant difference in the average INR (P=0.94).

Conclusion: Patients diagnosed with HRS-AKI with lower peak mean creatinine and mean admission total bilirubin and higher admission albumin that underwent treatment with albumin, midodrine, and octreotide had a higher rate of complete response.

Introduction

Hepatorenal syndrome (HRS) is a multisystem disorder occurring in those with advanced liver disease. HRS presents in decompensated liver cirrhosis with an incidence of 4%. The chance of HRS increases from 18% in the first year to nearly 40% in the fifth year. [1] Pathophysiology of HRS presents in the setting of cirrhosis inciting a neurohormonal changes that result in splanchnic and systemic vasodilation ultimately leading to renal hypoperfusion resulting in reflex renal vasoconstriction culminating in renal failure. [2] HRS can be characterized by acute kidney injury (AKI) with a high mortality (HRS-AKI), or by progressive renal function decline and refractory ascites with a better prognosis (HRS-non-AKI).[3]

HRS-AKI has a worse prognosis compared to HRS-non-AKI with only 10% of patients surviving longer than 90 days.[4] Diagnostic criteria for HRS-AKI include presence of (1) decompensated liver cirrhosis and ascites (2) AKI (3) no response of AKI after 2 days of volume expansion and holding diuretics (4) absence of shock and nephrotoxic agents (5) no evidence of structural kidney injury.[5] HRS-AKI (formerly known as Type 1 HRS) can be triggered by spontaneous bacterial peritonitis, gastrointestinal hemorrhage, major surgery or large volume paracentesis. Early diagnosis of HRS can allow for a better prognosis.[6]

Treatment of HRS-AKI includes prompt discontinuation of nephrotoxic medications, antihypertensives, diuretics and nonsteroidal anti-inflammatory drugs followed by initiation of vasoconstrictors and albumin. Vasoconstrictor options include terlipressin, norepinephrine or midodrine.[7] Reversal of HRS-AKI is defined by improved renal function achieving a complete response.[8]Review of the literature identifies factors that predict the chance of response of HRS-AKI to the above treatment modalities; however, there are only a few published studies primarily focusing on terlipressin, a therapy that is not universally available in the United States and was not approved by the FDA until 2022. These studies have shown that a higher change in mean arterial pressures, lower baseline bilirubin and creatinine levels, presence of systemic inflammatory response syndrome and lower urine neutrophil gelatinase-associated lipocalin (NGAL) were associated with response to terlipressin and albumin.[3] Studies evaluating predictive factors of HRS-AKI response to albumin plus norepinephrine or midodrine and octreotide are lacking.

This is a retrospective study performed prior to the FDA approval of terlipressin. Our aim was to identify factors predictive of response of HRS-AKI to albumin plus midodrine and octreotide. Identifying key lab values or other patient characteristics at the time of admission or during hospitalization can help to tailor treatment and establish an individualized management plan. This data may help select patients who would benefit from standard treatment or require more aggressive care. Furthermore, data from this study may identify patients who will not benefit from therapy allowing for more effective allocation of resources influencing hospital expenditure on treatment of HRS-AKI reducing treatment cost.

Methods and Data Analysis

A retrospective chart review was performed on 371 patients who were admitted with a primary diagnosis of decompensated cirrhosis and acute kidney injury per ICD-9/10 codes. Per International Club of Ascites (ICA) guidelines patients were diagnosed with AKI or non-AKI HRS[5].

Patients meeting ICA criteria for a diagnosis for HRS-AKI were included. Thereafter, the following inclusion criteria was established for our study: cirrhosis with ascites, an acute increase in Cr to greater than 2.5 mg/dL within a two-week span, absence of shock defined as systolic blood pressure (SBP) < 90 mmHg, no recent exposure to nephrotoxic agents, the absence of proteinuria (>500 g/dl) or pre-existing parenchymal disease, and no improvement in creatinine after discontinuation of diuretics and starting volume expansion. Exclusion criteria include cardiac, respiratory failure, cancer, or prior beta-blocker use for variceal bleeding. (Figure 1).

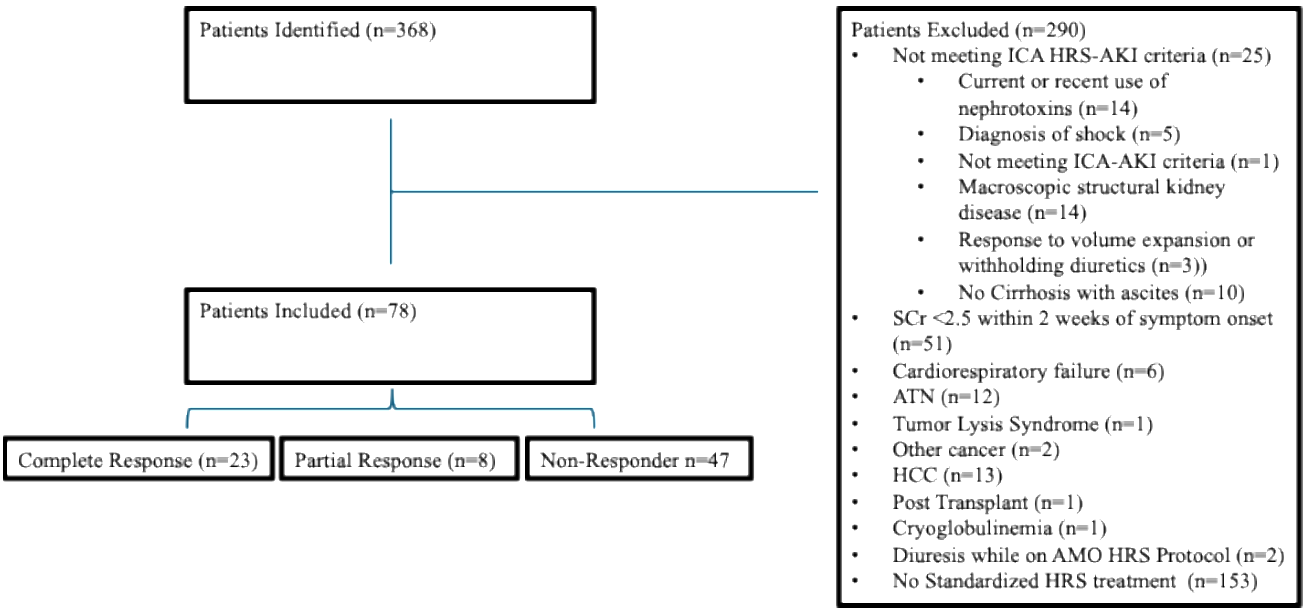

Figure 1: Flow diagram of patient enrollment

All patients were treated with albumin, midodrine, and octreotide. Following 3 days of therapy, patients were classified as demonstrating a complete response – decrease in Cr to < 1.5, partial response – decrease in Cr by > 50% from baseline but not to < 1.5, no response – no decrease or increase in Cr by day 3 of treatment. Treatment was continued beyond 3 days up to 14 days if the patient's Cr improved with therapy. Total bilirubin, albumin, and INR at admission and peak creatinine were compared among the different responder groups. Cutoff values for HRS-AKI reversal were expressed as mean values for complete response.

Statistics:

Categorical outcomes were evaluated using Fisher's exact or Chi-squared test, as appropriate. Categorical variables were expressed as percentages. Continuous parametric variables were evaluated with the two-tailed Student's t-test assuming unequal variance and nonparametric variables with Mann–Whitney U test. Normally distributed continuous variables were described as means and SD while skewed data were described as medians and interquartile ranges. Data analysis was conducted using SAS JMP Pro 13 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

78 patients met inclusion criteria of which 23 (29.49%) achieved a complete response, 8 (10.26%) had partial response, 47 (60.26%) were non responders. In complete responders 65.2% were male with an average age 59.0 ± 8.6, MELD-Na 28.5 ± 5.2, predominant cause of cirrhosis being alcohol 52.2%, and 52.2% of patients demonstrated >180-day survival. In partial responders 62.5% were male with an average age 63.8 ± 6.4, MELD-Na 28.1 ± 9.9, predominant causes of cirrhosis being alcohol 50.0% and HCV 50.0%, and 62.5% of patients demonstrated < 30-day survival. In non-responders 63.8% were male with an average age 56.6 ± 10.3, MELD-Na 28.7 ± 8.7, predominant causes of cirrhosis being alcohol 38.3% and HCV 23.4%, and 46.8% of patients demonstrated < 30-day survival. (Table 1).

	Groups by Response				
	Complete (n = 23)	Partial (n = 8)	Non-responder (n = 47)	P value (Complete vs. Non-responder)	P value (All Groups)
Sex (%male)	15 (65.2%)	5 (62.5%)	30 (63.8%)		0.99
Age (mean)	59.0 ± 8.6	63.8 ± 6.4	56.6 ± 10.3		0.13
Causes of Cirrhosis:					0.45
Alcohol	12 (52.2%)	4 (50%)	18 (38.3%)		
HCV	7 (30.4%)	4 (50%)	11 (23.4%)		
MAFLD/MASH	2 (8.7%)	0 (0%)	8 (17.0%)		
Other	2 (8.7%)	0 (0%)	10 (21.3%)		
HCC	3 (13.0%)	4 (50%)	4 (8.5%)		0.07
History of liver transplant	3 (13.0%)	1 (12.5%)	13 (27.7%)		0.31
History of TIPS	2 (8.7%)	1 (12.5%)	3 (6.4%)		0.4
MELD-Na on presentation (mean)	28.5 ± 5.2	28.1 ± 9.9	28.7 ± 8.7		0.98
Serum Cr on presentation	2.6 ± 1.9	2.1 ± 0.7	2.3 ± 1.4		0.49
Peak Cr	3.2 ± 1.7	3.2 ± 0.8	4.1 ± 1.6	0.04	0.07
T. bili on presentation	6.3 ± 4.7	9.7 ± 8.5	10.9 ± 11.8	0.02	0.19
Albumin on presentation	3.0 ± 0.6	2.7 ± 0.7	2.7 ± 0.5	0.03	0.08
INR on presentation	1.8 ± 0.6	2.1 ± 1.0	1.9 ± 0.9		0.6
Underwent hemodialysis	1 (4.3%)	4 (50%)	24 (51.1%)		< 0.01
Survival:					0.04
< 30 days	6 (26.1%)	5 (62.5%)	22 (46.8%)		
30-180 days	5 (21.7%)	2 (25%)	7 (14.9%)		
> 180 days	12 (52.2%)	1 (12.5%)	18 (38.3%)		

Table 1: Demographics

For complete, partial, and non-responders, the mean total bilirubin (mg/dL) in the respective groups were 6.27±4.72, 9.76±8.47 and 10.94 ±11.78. The mean albumin (g/dL) in each respective group were 3.04±0.60, 2.74±0.66 and 2.71±0.50. Mean INR were 1.90±0.91, 1.81±0.40, and 1.91±0.88. Mean Peak creatinine were 3.17±1.72, 3.24±0.84, and 4.05±1.61.

There was no significant difference in MELD-Na among the three groups. When compared to the no response group, the complete response group had a statistically significant difference with a lower total bilirubin (P=0.02) (Figure 2), higher albumin (P=0.03) (Figure 3), and lower peak creatinine (P=0.04) (Figure 4). There was no significant difference in the average INR (P=0.94).

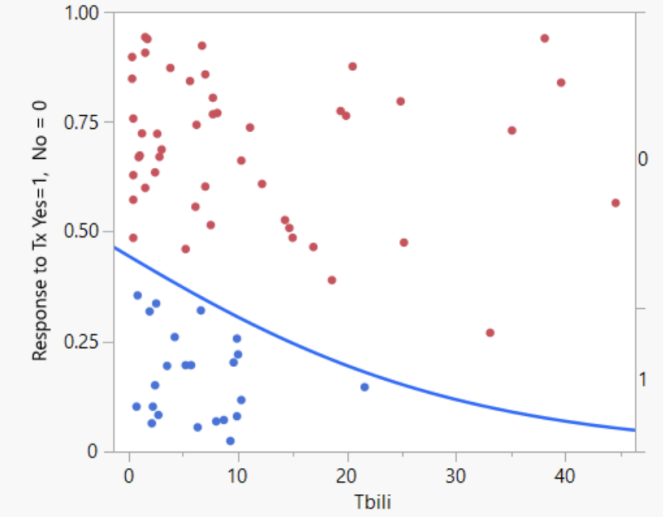

Figure 2: Comparison of mean total bilirubin between complete and non-responders

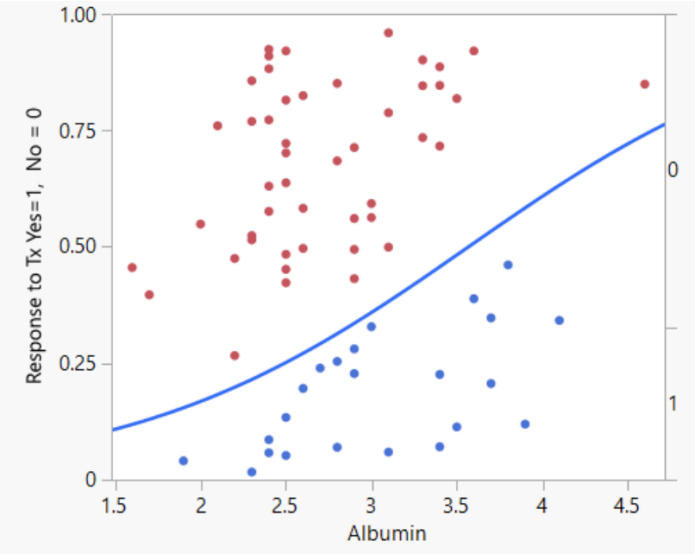

Figure 3: Comparison of mean albumin between complete and non-responders

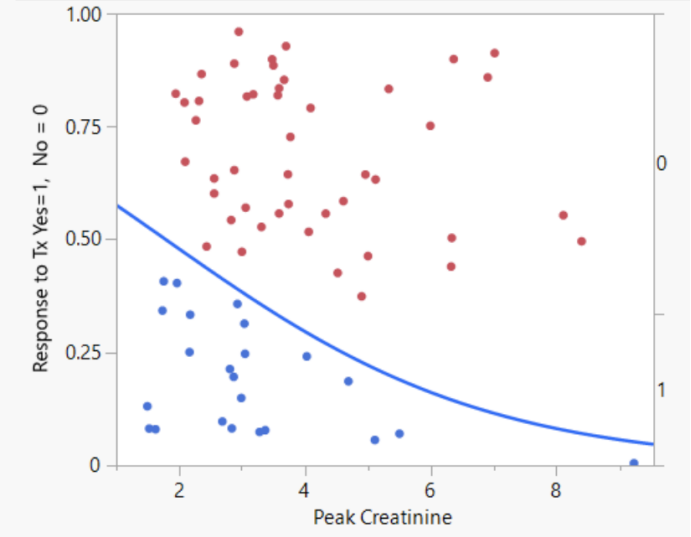

Figure 4: Comparison of mean peak creatinine between complete and non-responders

Discussion

There is a paucity of data defining factors predicting a complete response to treatment with midodrine, octreotide and albumin in HRS-AKI. We demonstrated variables predicting complete response to treatment of HRS-AKI with albumin, octreotide and midodrine to be serum levels with lower peak creatinine, lower total bilirubin and higher albumin levels. A cutoff value was demonstrated with a lower mean peak creatinine of 3.17±1.72 in complete responders indicating higher values less likely to completely respond to treatment. Similarly, cutoff values were demonstrated for mean total bilirubin (6.27±4.72) with higher values less likely to completely respond. A cutoff value for higher mean albumin levels (3.04±0.60) indicated lower levels were less likely to completely respond.

HRS-AKI that is not treated has a median survival of less than 10 days with the most definite therapy being liver transplant following initial medical therapy to achieve renal recovery and hemodynamic stability.[9] A review of 18 randomized control trials over 25 years up to 2023 focused on highlighting the extent of response to available HRS pharmacotherapy. All studies comprised varying primary endpoints although HRS reversal was defined similarly for all studies.[10,11]

Review of current literature defines variables predicting response to terlipressin based regimens for HRS-AKI. One such prospective study examined a cohort of 39 patients and 46% responded to terlipressin plus albumin. A serum total bilirubin <10 yielded a 67% response with corresponding values of increased mean arterial pressure MAP >or= 5mm Hg yielding a 73% response to treatment.[12] Another randomized control trial constituting terlipressin plus albumin versus placebo demonstrated serum creatinine to be the best predictor of response to therapy in the treatment group. The greatest benefit from treatment in the terlipressin arm was seen when baseline serum creatinine was <3.0 mg/dl with decreased change of response observed with higher creatinine levels and negligible response after 7 mg/dl suggesting no significant utility in advanced renal failure.[13] A retrospective study demonstrated that patients with 2 or more criteria qualifying systemic inflammatory response syndrome (SIRS) had a significantly higher response rate to terlipressin compared to placebo (42.9% vs 6.7%, P = 0.018).[14] It also demonstrated presence of SIRS at baseline (P=0.022) and change in renal resistive indices ΔRRI ≥5% by day 3 of treatment (P=0.048) to be independent predictors of HRS-AKI reversal in response to terlipressin. [14]These studies suggest that increased liver/kidney reserve, MAP, ΔRRI and presence of SIRS favor a response of HRS-AKI to terlipressin.

Limitations

This retrospective study comprised a small sample size which predisposes to risks of selection bias. We did not assess the concurrent use of home beta blockers prior to admission in patients which are known to reduce survival in patients with cirrhosis and refractory ascites. This study was performed prior to FDA approval of terlipressin. Future investigation would encompass evaluating concurrent beta blocker use as it relates to HRS-AKI response to treatment and survival.

Conclusion

In conclusion this study showed that patients who underwent HRS-AKI treatment with albumin, midodrine, and octreotide achieved a complete response with lower peak mean creatinine and mean admission total bilirubin and higher admission albumin. These findings contribute to identifying factors predictive of complete response to the standard treatment of HRS-AKI in the United States where there is a paucity of data regarding the subject. The ability to qualify patients as high or low probability to respond to standard treatment may potentially help in more effectively prioritizing low probability patients for liver transplant. Moreover, identifying patients that are of high probability to respond to medical therapy earlier may allow for expedited medical therapy for which response would be more favorable.

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