Original Research

The Hepatorenal Syndrome Patient Pathway: Retrospective Analysis of Electronic Health Records

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A B S T R A C T

Background: Hepatorenal syndrome (HRS) is among the leading causes of hospitalization and mortality in patients with chronic liver disease.

Objective: To assess the HRS patient journey from preadmission to postdischarge to understand patient characteristics, disease progression, treatment patterns, and outcomes.

Methods: We conducted a retrospective study using real-world data from a nationwide electronic health record database (Cerner Health Facts, Kansas City, Missouri). We used ICD-9/10 diagnosis codes to identify patients hospitalized with HRS between January 1, 2009, and January 31, 2018. We assessed patient characteristics and history, clinical presentation, treatment, and outcomes. Regression analysis was conducted to assess the association between patient characteristics and survival while adjusting for demographic and clinical covariates.

Results: The study included 3563 patients (62% men). Precipitants of HRS included gastrointestinal bleeding (18%), diuretics and infections (30%), and paracentesis (26%). Although 21% of patients had liver injury exclusively associated with alcohol use, 20% had hepatitis C, 8% had nonalcoholic steatohepatitis, and the etiology of the remainder (51%) was either some combination of conditions or unknown. A total of 42% of patients received vasopressors, including octreotide and midodrine (10%), other combinations of vasopressors (11%), or another single vasopressor (21%). In-hospital mortality was 34%, and 14% of patients were discharged to hospice. Regression analysis showed patients with acute-on-chronic liver failure had higher mortality in acute-on-chronic liver failure grades 1 (odds ratio = 1.59), 2 (odds ratio = 2.49), and 3 (odds ratio = 4.53) versus no acute-on-chronic liver failure. Among survivor patients, 38% were readmitted within 90 days of discharge; 23% of readmissions were HRS-related.

Conclusions: The HRS patient journey presented in this study highlights inconsistencies in, and provides insight into, associated hospital-based treatment strategies. A mortality rate of 34% along with a readmission rate of 23% associated with HRS-related complications warrant more disease awareness and effective treatment. Further research is needed to examine the interactions between the etiology of cirrhosis, precipitants, treatment, and outcomes. (Curr Ther Res Clin Exp. 2022; 82:XXX–XXX)

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Introduction

Hepatorenal syndrome (HRS) is characterized by the development of acute on subacute renal failure in patients with advanced chronic liver disease and is the leading cause of hospitalizations in the chronic liver disease disease group.1,2 Liver failure can occur due to alcoholic hepatitis, metastatic tumors, viral hepatitis, and other causes leading to multiple sequelae and ultimately renal vasoconstriction and HRS.3,4 Generally, HRS is associated with poor prognosis, with an estimated median survival of patients with untreated type 1 HRS to be 8 to 12 weeks, and a 25% survival probability after 30 days.1,5,6

Multiple markers can be examined to monitor the progression of HRS. Serum creatinine (SC) levels can aid in monitoring renal function and progression of HRS.7 Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh scores take into account international normalized ratio.8 Monitoring levels of hormones such as renin and aldosterone can also be clinically informative.8

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Based on the severity of disease, HRS is characterized into type 1 or 2. Type 1 HRS is characterized by the body's inability to maintain kidney perfusion and the rapid deterioration of kidney function. Type 1 HRS patients generally experience a rapid increase in Scr levels (>221 μmol/L in <2 weeks) and glomerular filtration rate <20 mL/min. Additionally, patients with type 1 HRS are associated with a poor prognosis with a median survival rate of only 8 to 12 weeks. Type 2 HRS is a less severe form of renal impairment, marked by diuretic-resistant ascites. These patients have initial Scr levels <221 μmol/L. Type 2 HRS follows a more gradual progression and is associated with the advancement of cirrhosis and a median survival time of approximately 6 months.

Patients with HRS are complex and typically have a number of other hepatic- and renal-centric diagnoses that complicate the diagnosis of HRS and its influence. This study characterizes the HRS patient pathway, which highlights patient characteristics and history, clinical presentation, treatment patterns, and key outcomes associated with HRS before and after hospitalization in a large US electronic health records (EHR) database that includes patients from all payer types. Regression analysis was conducted to assess the association between patient characteristics and survival in patients while adjusting for demographic and clinical covariates.

After data analysis, we developed Sankey diagrams, which show metric flows and categorical relationships to provide an in-depth look at the patient journey from admission to discharge.

Participants and Methods

We performed a retrospective longitudinal study with data from January 1, 2009, to January 31, 2018, using a large US EHR database comprising >700 clinical facilities and hospital systems (Cerner HealthFacts; Kansas City, Missouri). This study was granted exemption from institutional review board oversight by Western IRB (Olympia, Washington).

Patients with HRS were identified by the ninth revision of the International Statistical Classification of Diseases and Related Health Problems code 572.4 (Hepatorenal syndrome) and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems code K76.7 (Hepatorenal syndrome), admitted between January 1, 2009, and January 31, 2018, and discharged before January 31, 2018. For study inclusion, adult patient records (age 18 years or older) were required to contain at least 2 Scr readings at different times during the index hospitalization period. Patients with missing, null, or invalid discharge care setting or discharge disposition data were excluded. The first visit where patients met all inpatient inclusion criteria was considered the index hospitalization date.

Patients with a recorded hemodialysis procedure and/or transjugular intrahepatic portosystemic shunt within a month before hospitalization, or who died <24 hours post/alternative vasopressor therapy initiation (terlipressin is not available in United States), or had a record of a prior liver transplant, or hospitalization with HRS (as defined above) during the 6 months before the HRS episode within the observational window were excluded.

Patient data were captured from EHRs, including patient characteristics and history (prior cirrhosis-related admissions), clinical presentation (etiology of cirrhosis, precipitants, care settings, and labs), treatment (medications and procedures), and key outcomes (discharge status, follow-ups, and readmissions). In addition to basic patient demographic characteristics, we described the etiology/relevant medical history before the index hospitalization, and payer characteristics. We included hospital characteristics, complications of liver disease, several scoring systems for severity of disease, mortality, and prognosis (eg, Acute Physiology and Chronic Health Evaluation II, Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury [KDIGO-AKI], MELD, Child-Turcotte-Pugh, and chronic liver failure-sequential organ failure assessment), high-cost procedures (eg, transfusion of blood products, mechanical ventilation, hemodialysis and other renal replacement therapies [RRTs], transjugular intrahepatic portosystemic shunt, paracentesis, and liver or combined kidney and liver transplant).

Clinical outcomes included administration of medication (ie, albumin, vasopressors, octreotide, diuretics, beta blockers, and rifaximin) and measurement of renal function via Scr. Clinical and administrative outcomes through 90 days postindex included mortality (index hospitalization, and 30, 60, and 90 days), readmission within 90 days, length of intensive care unit (ICU) stay and major comorbidities.

Before analysis, data cleaning included removing identical and duplicate entries, omitting visits with inconsistent admission and discharge time stamps, and removal of patients with missing demographic and administrative data.

Baseline patient characteristics were summarized via counts and percentages for binary or categorical variables and with means and SDs, or via medians and 25th to 75th percentiles for continuous variables. A logistic regression model was used to determine the association between acute-on-chronic liver failure (ACLF) grade and mortality; adjusting for demographic characteristics (gender, race, and index year), clinical characteristics (age-adjusted Charlson Comorbidity Index, length of hospital stay, presence of ICU stay, admission type, transfusion, dialysis, ventilation, Scr level, and cirrhosis in the past 180 days), hospital characteristics (bed size, US census region, and urban or rural residence), and medication used (diuretics, rifaximin, vasopressors, paracentesis, octreotide, and midodrine).

We used odds ratios (ORs) from logistic regressions to quantify the associations of ACLF grade with mortality. Our comprehensive multihospital data allowed us to extensively adjust the models for a priori defined and potential confounders, including patient demographic characteristics, clinical characteristics, and hospital characteristics and reduce the chances of residual confounding. Adjustments had no null values because we removed patients with missing demographic and administrative data during the study cohort selection phase. We did not discard any attribute from the models because we found low correlation between the adjustments based on the variation inflation factors. Furthermore, there was no evidence of multicollinearity among adjustments because the variation inflation factors were all far <2.5. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) with alpha set at 0.05.

Results

Demographic characteristics

We identified 33,09 adult patients (aged 18 years or older) in the database with a length of stay ≥48 hours, Scr values, and the ninth revision International Statistical Classification of Diseases and Related Health Problems code of 572.4 (10th revision code K76.7) for HRS. Patient demographic and clinical characteristics at the time of admission and hospital-specific characteristics were analyzed. Most patients (n = 1519; 45.9%) were between ages 50 and 64 years (mean age = 59.4 years), men (n = 2045; 61.8%), and Caucasian (n = 2422; 73.2%). Although 1154 (34.9%) and 598 (18.1%) of patients were on Medicaid and Medicare respectively, 778 (23.5%) had commercial insurance.

The vast majority of admissions in this study were categorized as emergency (n = 2662; 80.5%), indicating that these patients required immediate assessment and/or treatment. Approximately three-fourths of all hospitals analyzed were teaching fa-
cilities (n = 2447; 74.0%) and 27.1% (n = 898) had a bed size ≥500 (Table 1).

**Patient history**

Although all patients were diagnosed with cirrhosis at the inclusion of the study, at the time of admission, 701 (21.2%) patients had alcoholic hepatitis, 646 (19.5%) had hepatitis C, 514 (15.5%) had nonalcoholic steatohepatitis, and 1378 (41.6%) had alcoholic cirrhosis (not mutually exclusive) (Table 1). Furthermore, whereas 49% of patients had an identifiable etiology, the majority of patients (51.0%) had severe comorbidities (eg, ascites and encephalopathy) without identifiable etiology, underscoring the difficulties in understanding how patients develop cirrhosis and subsequently, HRS (see Supplemental Figure 1).

More than one-half of the study population (62.4%) had a baseline institutional encounter with a cirrhosis claim during the baseline period (180 days before or at index hospitalization). Before HRS diagnosis, mean (SD) inpatient and outpatient visits per patient were 2.7 (4.3) and 11.0 (23.2), respectively. Mean number of cirrhosis related visits preindex was 5.0 (10.6).

Ascites requiring paracenteses and gastrointestinal bleeding, both of which are precipitants of HRS, were identified in 50.4% (n = 1669) and 32.8% (n = 1085) of patients, respectively. Other, less common precipitants during index included diarrhea (n = 197; 6.0%), spontaneous bacterial peritonitis (n = 431; 13.0%), hypovolemia (n = 136; 4.1%), diuretics (n = 1383; 41.8%), and other infections (n = 2275; 68.8%) (Table 1).

**Admission and inpatient stay**

Due to the complex nature of these patients and a multitude of interactions between different therapies, it is difficult to measure the influence of developing AKI or receiving vasopressor treatment with final patient outcomes. Therefore, several established prognostic indicators of HRS were assessed.

HRS patients had a mean (SD) Charlson Comorbidity Index of 8.6 (3.6) and Acute Physiology and Chronic Health Evaluation (APACHE) III score of 66.8 (26.2). Patients were assessed for AKI with KDIGO-AKI staging, and 41.3% (n = 1365) were assessed as stage 3. Liver function abnormalities were analyzed by utilizing ACLF grading and 34.1% (n = 1126) of patients were characterized as grade 3. Mean change (SD) in MELD score for patients between baseline and admission was 1.3 (10.6) (Table 2).

**Treatment**

During index hospitalization, patients were treated with albumin (n = 1966, 59.4%; 19.9% albumin only and 39.5% vasopressors + albumin), vasopressors excluding midodrine (n = 1072; 32.4%), midodrine in combination with octreotide (n = 1131; 34.2%). Among the vasopressors used, excluding midodrine, norepinephrine was used the most (n = 454; 13.7%), followed by phenylephrine (n = 245; 7.4%), and epinephrine (n = 182; 5.5%). Patients were also treated with rifaximin (n = 1048; 31.7%), pentoxyfylline (n = 177; 5.4%), and beta blockers (n = 1162; 35.1%). Before being hospitalized for HRS, 4.8% of patients received vasopressors, and 7.0% received midodrine in combination with octreotide, suggesting that these patients may have encountered severe hepatic and renal dysfunction. After discharge, 16.2% of patients received vasopressors during readmission. Additionally, 19.5% of patients continued to receive albumin, and 6.4% continued to receive midodrine in combination with octreotide (see Supplemental Figure 2).

Table 1 - Demographic, clinical, and hospital characteristics, etiologies, and hepatorenal syndrome (HRS) precipitants (N = 3309).

| Variable | Result |
|----------|--------|
| **Demographic characteristics** | |
| Age, y | 18–29 33 (1.0) |
| 30–49 | 662 (20.1) |
| 50–64 | 1519 (45.9) |
| 65+ | 1205 (35.1) |
| Mean (SD) | 59.4 (12.7) |
| Sex | Male 2045 (61.8) |
| Ethnicity | Caucasian 2422 (73.2) |
| | African American 361 (10.9) |
| | Asian/Pacific Islander 47 (1.4) |
| | Other 368 (11.1) |
| | Not specified 65 (2.0) |
| | Hispanic 46 (1.4) |
| **Clinical characteristics** | |
| Currently smoking (at index) | 1033 (31.2) |
| Payer type | Commercial 778 (23.5) |
| | Medicaid 508 (16.1) |
| | Medicare 1154 (34.9) |
| | Other: Government or military 94 (2.8) |
| | Other: Nongovernment or worker’s compensation 28 (0.9) |
| | Self 131 (4.0) |
| | Not specified 526 (15.9) |
| **Admission type** | |
| Emergency | 2662 (80.5) |
| Urgent | 376 (11.4) |
| Elective | 200 (6.0) |
| Not specified | 65 (2.0) |
| Other | 5 (0.2) |
| **Admission source** | |
| Physician or clinical referral | 1818 (54.9) |
| Emergency room | 753 (22.8) |
| Hospital or facility transfer | 421 (12.7) |
| Not specified | 300 (9.1) |
| Other | 17 (0.5) |
| **Hospital characteristic** | |
| Teaching facilities | 2447 (74.0) |
| Acute care hospitals | 3306 (99.9) |
| Bed size | 500+ 898 (27.1) |
| 200-299 | 884 (26.7) |
| 100-199 | 872 (26.4) |
| 0-99 | 469 (14.2) |
| | 186 (5.6) |
| **Census region** | |
| South | 1133 (34.2) |
| Northeast | 1032 (31.2) |
| West | 689 (20.8) |
| Midwest | 454 (13.7) |
| **Etiology** | |
| Alcoholic hepatitis | 701 (21.2) |
| Hepatitis C | 646 (19.5) |
| Nonalcoholic steatohepatitis | 514 (15.5) |
| Alcoholic cirrhosis | 1378 (41.6) |
| **Precipitants of HRS** | |
| Gastrointestinal bleeding | 1085 (32.8) |
| Diarrhea | 197 (6.0) |
| Hypovolemia | 136 (4.1) |
| Diuretic use | 1422 (43.0) |
| Paracentesis | 1669 (50.4) |
| Spontaneous bacterial peritonitis | 431 (13.0) |
| Other infections | 1564 (47.3) |

* Values are presented as n (%), unless otherwise noted.
† Not mutually exclusive.

A subgroup analysis found that as patients progressed through more severe AKI staging and MELD groups, use of vasopressors also increased (Table 3).
Table 2

Improvements and changes in serum creatinine (SCr) level and Model for End-Stage Liver Disease (MELD) score from baseline (n = 3309).

| Variable | Result |
|----------|--------|
| SCr level at baseline (mg/dL) | |
| <1.5 | 1028 (31.1) |
| 1.5 to <2.25 | 834 (25.2) |
| 2.25 to <3.0 | 514 (15.5) |
| 3.0 to <4.0 | 406 (12.3) |
| ≥4.0 | 527 (15.9) |
| Patients with SCr level improvement posttreatment | |
| Improvement >50% | 1859 (56.2) |
| Improvement 31%-50% | 529 (16.0) |
| Improvement <30% | 608 (18.4) |
| No change | 313 (9.5) |
| SCr level posttreatment (mg/dL) | |
| >1.5 | 2,823 (85.3) |
| ≤1.5 | 486 (15.0) |
| Change in MELD score | |
| From baseline to index hospitalization | 1.3 (10.6) |

Values are presented as n (%).

Outcomes

Baseline SCr values are shown in Table 2. SCr level improvement was measured using 2 parameters. A total of 2388 patients (72%) had SCr improvement >31% but only 486 patients (15%) had a SCr decrease to ≤ 1.5 mg/dL posttreatment (Table 2). Of the 1507 (45.5%) patients who received vasopressors, 183 patients (12.1%) had >50% improvement in renal function, and 163 (10.8%) patients had improved renal function between 31% and 50%. A small number (n = 91; 6.0%) had no change in renal function, and almost half of the patients (n = 731; 48.5%) had worsening renal function. From these results, we may infer that patients with worsening SCr levels during their inpatient stay were more likely to die and patients who experienced improvement in their SCr level by at least 30% during their stay were more likely to survive (see the Figure 1).

Regression analysis showed that patients with ACLF had increasing mortality rate with increasing ACLF grade 1 (OR = 1.59; 95% CI, 1.09–2.30), 2 (OR = 2.49; 95% CI, 1.73–3.60), and 3 (OR = 4.53, 95% CI, 3.11–6.58) versus no ACLF (Table 4). Nearly half of the patient population admitted for HRS was transferred to an ICU (n = 1460; 44.1%). The average (SD) length of stay among surviving hospitalized patients with HRS (n = 2176) was 10.9 (11.6) days and the average ICU length of stay among survivors was 6.9 (7.6) days (median = 4.2 days; n = 769). Discharge disposition from index hospitalizations showed that 34.2% (n = 1133) of patients died in the hospital and 14.4% (n = 475) were discharged to hospice. A large percentage of patients (39.7%) who received vasopressors or RRT died in the hospital (see Supplemental Figure 3). The 90-day mortality rate climbed to 40% (n = 1,331).

A total of 1701 patients survived their index hospitalization (ie, did not die or receive a discharge to hospice). Among the survivors, 54.7% (n = 931) were discharged home, 20.3% (n = 345) to a postacute-care setting, 16.7% (n = 284) to a skilled nursing facility, and 6.0% (n = 102) to an inpatient hospital setting. Analysis of posthospital discharge data of surviving patients revealed that 37.9% (n = 824 of 2173) of patients were readmitted to the hospital within 90 days of discharge, with an average time to readmission of 22.0 days. For HRS-related admissions, surviving patients returned to the hospital after an average of 19.5 days (n = 176; 22.9% of 769), and for non-HRS-related admissions, after 22.8 days (n = 593; 77.1% of 769) (see Supplemental Figure 3).

Discussion

This study represents an analysis of the HRS patient journey, from etiology leading to admission and key outcomes after the first, or index, HRS hospitalization. The mortality rate among hospitalized patients with HRS seen in this study (34%) approaches the mortality rate observed in a previous retrospective analysis conducted with hospitalized HRS patients between 2009 and 2015 (37%). However, our analysis contained a larger proportion of patients with precipitants of paracentesis, hypovolemia, and spontaneous bacterial peritonitis before index hospitalization.

ACLF has also previously been reported to be associated with high short-term mortality. Our analysis additionally revealed this mortality risk to proportionately increase with ACLF scoring among patients with HRS.

In terms of clinical outcome, only 15% of patients showed a decrease in SCr values to a level of ≤ 1.5 mg/dL posttreatment, a parameter that has previously been classified as complete response among patients with HRS. Furthermore, due to the heterogeneity within patients with HRS, our visualization helps convey that treatment strategies are not uniform within this patient population, suggesting that the underlying etiology of cirrhosis in HRS patients, alcohol use, nonalcoholic steatohepatitis, and viral hepatitis, in addition to initial presentation in the inpatient setting, may have affected treatment selection, clinical response (HRS reversal), and outcomes.

This in-depth investigation of the HRS patient journey identifies possible entry points for optimizing the management of these patients, including earlier diagnosis and earlier effective treatment options such as vasopressors before ICU admission. The study also serves as an important visual addition to our understanding of the complex flow of treatment strategies associated with HRS using Sankey diagrams.

Table 3

Patients’ Kidney Disease: Improving Global Outcomes for Acute Kidney Injury (KDIGO-AKI) stage and Model for End-Stage Liver Disease (MELD) score levels by treatment during index admission.

| Variable | Albumin | Vasopressors | Midodrine and Octreotide | Beta blockers |
|----------|---------|-------------|--------------------------|--------------|
| KDIGO-AKI stage | | | | |
| No AKI (n = 601) | 271 (45.1) | 20 (3.3) | 119 (21.3) | 211 (35.1) |
| Stage 1 (n = 944) | 552 (58.5) | 69 (7.3) | 307 (32.5) | 339 (35.9) |
| Stage 2 (n = 399) | 244 (61.2) | 43 (10.8) | 130 (32.6) | 149 (37.3) |
| Stage 3 (n = 1365) | 899 (65.7) | 175 (12.8) | 555 (40.7) | 463 (33.9) |
| MELD score | | | | |
| ≤10 (n = 127) | 50 (39.4) | 19 (15.0) | 23 (18.1) | 60 (47.2) |
| 11–18 (n = 641) | 352 (54.9) | 46 (7.2) | 185 (28.9) | 289 (45.1) |
| 19–24 (n = 616) | 350 (56.8) | 50 (8.1) | 191 (31.0) | 233 (37.8) |
| ≥25 (n = 1821) | 1,153 (63.3) | 185 (10.2) | 698 (38.3) | 549 (30.1) |
| Unknown (n = 104) | 61 (58.7) | 7 (6.7) | 34 (32.7) | 31 (29.8) |

Values are presented as n (%).

For the purpose of analysis, we assumed that if midodrine was given to patients with hepatorenal syndrome, octreotide was given as well.
This study has certain limitations that should be considered when evaluating the presented results. The data used in this analysis cover an extensive, but inherently limited sample of US hospitals, that may not be generalizable to the entire US hospital population. For our analysis, we rely heavily on the precision of the diagnosis codes to segment out the patients with or without HRS, as well as to identify specific comorbidities and track accurate outcomes. Errors in coding could result in patients who may not meet the specific inclusion criteria. Longitudinal tracking of some patients may not be possible if the patients transitioned to care facilities that do not contribute to the dataset. Patients who had no preexisting cirrhosis codes and presented to the hospital with HRS...
were likely previously treated at a facility that does not contribute to the Cerner database.

Conclusions

Our findings illustrate the current treatment of HRS in US hospitals and highlight the significant unmet need because 46.5% of patients did not receive treatment with vasopressors or RRT. Although 42% of patients with HRS had alcoholic cirrhosis and 21% had alcoholic hepatitis, most patients have a more complex disease history with comorbid conditions. The mortality and readmission rates reported in our study among patients with HRS support the need for better disease awareness and more effective treatment options, considering only 15% of patients showed improvements in SCR level to ≤ 1.5 mg/dL posttreatment. Further research is needed to examine the factors that influence the resolution of HRS, in addition to the interactions between cirrhosis etiology, HRS precipitants, and outcomes stratified by HRS risk.

Conflicts of Interest

This study was funded by Mallinckrodt Pharmaceuticals. K. Jamil and X. Huang are employees of Mallinckrodt Pharmaceuticals. D. Hayashida and K. Lodaya are employees of Boston Strategic Partners, Inc.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2022.100663.

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