

Impact of Transfer Status on Outcomes in Hospitalized Patients with Hepatorenal Syndrome

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ABSTRACT

AIM: To examine the impact of transfer status on outcomes in patients hospitalized with hepatorenal syndrome (HRS) at the population level.

MATERIALS AND METHODS: Using a national database, we performed a retrospective study on all adult (≥ 18 years) with HRS between 2012-2014. All hospitalizations involving any form of chronic kidney disease were excluded. The primary outcome was in-hospital mortality and the secondary outcomes were chronic liver

disease complications, procedure utilization, length of hospital stay, and hospitalization, cost. Outcomes were compared between those who were directly admitted and those who were transferred from another hospital.

RESULTS: 49,190 hospitalizations met the inclusion criteria with 8,160 (16.5%) in the transfer group. The transfer group had higher mortality (41.5% vs 36.0%). On multivariate logistic regression, the transfer group had significantly higher odds of mortality (odds ratio [OR] 1.36, 95% confidence interval [CI] 1.21 - 1.53), spontaneous bacterial peritonitis (OR 1.37, 95% 1.17 - 1.59), hepatic coma (OR 1.18, 95% CI 1.05 - 1.32), dialysis (OR 1.97, 95% CI 1.68 - 2.30), transjugular intrahepatic portosystemic shunt (OR 1.77, 95% CI 1.15 - 2.72), liver transplant (OR 2.59, 95% CI 1.97 - 3.40), and incurred an incremental cost of \$9,693 (\$6,023 - \$13,363). However, the odds of variceal bleeding and incremental length of stay were not statistically significant.

CONCLUSION: Patients transferred with HRS to another hospital had worse outcomes compared to directly admitted patients and incurred higher hospitalization costs.

Key words: Chronic liver failure; Hepatorenal Syndrome; Interhospital transfer.

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Abbreviations: CI: confidence interval; HRS hepatorenal syndrome; IHT: interhospital transfers; LOS: length of Stay; NIS: National Inpatient Sample; OR: odds ratio; SBP: spontaneous bacterial peritonitis; TIPS: transjugular intrahepatic portosystemic shunt

INTRODUCTION

Hepatorenal syndrome (HRS) is a life-threatening complication of

chronic liver disease (usually seen in patients with advanced cirrhosis and ascites) and acute liver failure and associated with high short-term mortality^[1,2]. Patients with type 1 HRS have more severe liver and renal failure, and therefore have worse outcomes compared with type 2 HRS patients. The median survival in type 1 HRS patients is 1 month compared with 6.7 months in type 2 HRS patients^[2]. Liver transplantation remains the only effective treatment for both type 1 and type 2 HRS. As a bridge to liver transplantation, some patients require transjugular intrahepatic portosystemic shunt (TIPS) and renal replacement therapy and sometimes extracorporeal albumin dialysis. As such, these patients require immediate transfer to centers where these procedures can be offered. However, there is no data on the impact of transfer status on clinical outcomes in HRS patients at the population level.

There is robust literature showing worse clinical outcomes and higher hospital cost in transferred patients compared to those who were directly admitted, especially in those requiring intensive care unit level of care^[3-6]. More importantly, interhospital transfers (IHT) for emergency procedures like percutaneous coronary intervention and endovascular treatment for acute ischemic stroke resulted in worse clinical outcomes in the transfer group^[7,8]. A similar phenomenon was also observed in general surgery admissions. A study using the American College of Surgeons National Surgery Quality Improvement Program found that interhospital transfer is an independent risk factor for mortality, morbidity, and high resource utilization^[9]. These worse outcomes could be due to delay in diagnosis and initiation of transfer, availability of bed space in the receiving hospital, medical errors from transition of care, and the complex logistics of IHT^[10-13].

Despite the assumption that the risk-benefit ratio favors IHT for HRS patients, the delay in presenting to tertiary centers could potentially lead to worse outcomes. Therefore, using the United States National Inpatient Sample (NIS) database, we conducted a retrospective study to examine the impact of transfer status on clinical outcomes and hospital resources utilization in patients with HRS. We hypothesized that in-hospital mortality, rate of chronic liver disease complication, hospitalization cost, and length of stay is higher in the transfer group compared to non-transfer group.

METHODS

Data Source

We queried the 2012 - 2014 NIS database to identify patients with HRS. The NIS database contains a 20% stratified random sample of all U.S. hospitals discharges, which approximates a total of 8 million discharges yearly^[14]. This is a publicly available de-identified dataset and therefore exempted from Institutional Review Board review. Data use was performed in accordance with the NIS data agreement.

Study Population

We included all patients ≥ 18 years of age who were admitted with the diagnosis of HRS in our analysis using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9 CM) [ICD] code 572.4. All patients with end stage renal disease (ICD-9 CM code 585.6) and chronic kidney disease (using clinical classification software code 158) were excluded. Additionally, all patients admitted for creation of arteriovenous fistula were excluded from the study population. All other diagnosis codes used in this study are shown in Table 1. Only observations with complete data on age, gender, race, insurance status, total hospital charge, transfer status, length of stay, and disposition (e.g. inpatient mortality) were

included in the final analysis.

Study Variables

This analysis included patient demographic and clinical data including age, sex, race, month and year of hospital admission, length of stay, primary and secondary diagnoses, procedures, disposition (e.g., inpatient death), national quartile of the median household income for patient's zip code, charlson comorbidity index, and insurance status. Hospital characteristics including hospital region and hospital bed size were also included.

Outcome Variables

Our primary outcome was all-cause in-hospital mortality. The secondary outcomes were rate of chronic liver disease complications, rate of procedure utilization, length of stay (LOS), and total hospitalization cost. The total charges reported in the database was converted to cost using the cost-to-charge ratio provided for each hospital and adjusted for inflation using 2014 as the base year.

Statistical Analysis

Continuous variables were reported as means with standard errors and categorical variables were reported as percentages. Pearson's chi-squared test and Student *t*-test were used to evaluate categorical and continuous variables respectively. Logistic regression was used to examine the association between transfer status and in-hospital mortality. For our variable selection, only variables with *p*-value less than 0.2 on univariate analyses were included in the logistic regression model. These variables are: age, hospital region, hospital bed size, insurance status, variceal bleeding, hepatic coma, sbp, dialysis, and liver transplantation. These same variables were included in further regression analyses. We estimated the odds of chronic liver disease complications (SBP, Hepatic coma, and variceal bleeding) and the odds of procedures (TIPS, dialysis, and liver transplantation) in the transfer group. Lastly, using linear regression, we modelled the relationship between transfer status and LOS and hospitalization cost in the transfer group.

Stata version 15.1 (StataCorp LP, College Station, TX) was used for all analyses. We accounted for the stratified cluster sampling design and incorporated discharge-level weights to produce national estimates with 95% confidence intervals (Cis) in all analyses. *P* values less than 0.05 was used as the threshold for statistical significance.

RESULTS

49,190 hospitalizations for HRS met the inclusion criteria during the study period. 8,160 (16.5%) were in the transfer group while

Table 1 ICD codes.

Disease	ICD-9
Hemodialysis/Hemofiltration	V56.0, V56.1, 54.98, V45.11, V45.1, 39.95
End stage renal disease	585.6
Variceal bleeding	456.0, 456.1, 456.2, 531.4, 532.4, 456.80, 578.9, 578
TIPS	39.1
Liver transplantation	50.5, 50.59
SBP	567.23
Hepatorenal syndrome	572.4
Ascites	789.5
Hepatic coma	572.2
HIV/AIDS	042, 079.53

41,030 (83.5%) were in the non-transfer group. Baseline patient demographics are shown in Table 2. Baseline clinical characteristics are shown in Table 3. There was no remarkable difference in the mean age between the study cohorts. There were more males in the non-transfer group (63.8% vs 59.6%) and the overwhelming majority was Caucasian (73% in the transfer group and 63.8% in the non-transfer group). The proportion of the uninsured population was lower in the transferred group (6.6% vs 9.0%) and most of the patients were managed in large bed sized hospitals (75.7% of transfer group and 59.7% of the non-transfer group). The overwhelming majority (85.1%) of the transfer group was managed in teaching hospitals compared to the 59.1% of the non-transfer group that was managed in teaching hospitals.

The overall in-hospital mortality was 36.9% and was higher in the transfer group (41.5% vs 36.0%). At baseline, the transfer group had a higher proportion of spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, ascites, and variceal bleeding, and a higher procedure utilization (TIPS, dialysis, and liver transplantation). There was no significant difference in the proportion of HIV/AIDS between the two groups (Table 2). The average LOS in days was higher in the transfer group (14.7 ± 0.51 versus 10.5 ± 0.15); hospitalization costs were also higher for transfers compared to the non-transfer group (\$56,297 ± 3,422 versus 31,031 ± 738).

On multivariate regression, the adjusted odds of SBP (OR 1.37, 95% CI 1.17 - 1.59), hepatic coma (OR 1.18, 95% CI 1.05 - 1.32), dialysis (OR 1.97, 95% CI 1.68 - 2.30), TIPS (OR 1.77, 95% CI 1.15 - 2.72), and liver transplant (OR 2.59, 95% CI 1.97 - 3.40) were higher in the transfer group compared to the non-transfer group. However, the adjusted odds of variceal bleeding was not statistically significant (See Table 4). The transfer group had a significantly higher odds of mortality (OR 1.36, 95% CI 1.21 - 1.53) (Table 4) and incurred an incremental cost of \$9,693 (\$6,023 - \$13,363) per hospitalization compared to the non-transfer group. However, the incremental LOS was not statistically significant (1.54 days, 95% CI 0.81 - 2.27). Of note, in the multivariate mortality model, liver transplantation markedly reduced the risk of in-hospital mortality (OR 0.09, 95% CI 0.06 - 0.13) while dialysis conferred a higher risk of in-hospital mortality (OR 2.39, 95% CI 1.09 - 2.74) in the overall HRS population, irrespective of the transfer status. In the same model, TIPS also reduced the odds of in-hospital mortality, but not statistically significantly (OR 0.69, 95% CI 0.44 - 1.07) (Table 5).

DISCUSSION

The high short-term mortality and the expertise required for the life-saving procedures in HRS make timely transfer to tertiary centers the cornerstone of management. Therefore, we hypothesized that patients transferred to other facilities would have higher rates of chronic liver disease complications, dialysis, TIPS, liver transplantation, mortality, and would incur a higher hospitalization cost due to potential delay in diagnosis and the challenging logistics involved in an IHT. The findings of this study confirmed our hypotheses for all outcomes except for the variceal GI bleeding and length of stay.

The patients in the transfer group were younger and more likely to be white. They were also more likely to be managed in a teaching hospital with a large bed size. The patients in the transfer group were less likely to be black, Hispanic, uninsured. Other similar studies that examined geographic and racial disparities in inter-hospital intensive care unit transfers found that black and Hispanic race and older age were associated with a lower likelihood of IHT^[15]. Race and insurance status were found to have no association with outcomes in our study. We expected the transferred group to have greater

Table 2 Demographic characteristics.

N = 49,190	Transfer group (n = 8,160)	Non-transfer (n = 41,030)	p value
Age in years (Mean ± SE)	56.16 ± 0.32	57.61 ± 0.14	<0.01
Male, %	59.62	63.83	<0.01
Race, %			
White	72.98	68.55	<0.01
Black	8.46	10.68	
Hispanic	9.93	14.01	
Asian/Pacific Islander	1.78	2.01	
Native Americans	2.08	1.4	
Others	4.78	3.35	
Charlson Comorbidity Index	4.03 ± 0.04	4.49 ± 0.02	<0.01
Insurance (%)			
Medicare	35.66	36.74	<0.01
Medicaid	25.8	25.05	
Private	31.92	29.17	
Uninsured	6.62	9.03	
Median zip code income, %			
1st quartile	31.3	30.16	
2nd quartile	27.08	25.95	
3rd quartile	24.56	23.96	
4th quartile	17.07	19.93	
Hospital Region, %			
North East	22.98	20.57	0.02
Midwest	20.77	16.78	
South	36.15	38.26	
West	20.1	24.38	
Bedside, %			
Small	5.45	13.66	<0.01
Medium	18.87	26.63	
Large	75.67	59.71	
Transferred out, %	26.59	29.21	0.000
Teaching Status, %			
Teaching	85.11	59.12	< 0.01

Table 3 Baseline clinical characteristics (reported in percentages except for length of stay and cost).

	Transferred-in (n = 8,160)	Non-transfers (n = 41,030)	p value
SBP	16.18	11.46	<0.01
Hepatic coma	45.65	39.56	<0.01
Liver transplant	9.07	2.69	<0.01
Variceal bleeding	6.5	5.9	0.35
TIPS	2.45	1.04	<0.01
Dialysis	22.37	11.6	<0.01
Ascites	67.03	63.01	0.02
HIV/AIDS	0.67	0.84	0.5
Died	41.48	35.95	<0.01
Length of stay in days (mean ± sd)	14.73 ± 0.51	10.50 ± 0.15	<0.01
Hospital Cost in 2014 US\$ (mean ± sd)	56,297 ± 3422	31,301 ± 738	< 0.01

illness severity, but the comorbidity index is higher in the non-transfer group. This can be explained by the older age and the higher proportion of uninsured and racial minority in the non-transfer group. Interestingly, the comorbidity index has no association with any of the outcomes.

Patients with HRS are usually referred to tertiary centers for consideration of liver transplantation, which remains the definitive

Table 4 Adjusted odds ratios for complications and procedures

Covariates	Adjusted OR (95% CI)
Variceal bleeding	1.02 (0.81 - 1.28)
SBP	1.37 (1.17 - 1.59)
Hepatic coma	1.18 (1.05 - 1.32)
Liver transplant	2.59 (1.97 - 3.40)
TIPS	1.77 (1.15 - 2.72)
Dialysis	1.97 (1.68 - 2.30)

treatment. It is expected that the referrals would not be accepted if a patient is not eligible for transplant. This explains the higher rate of liver transplantation in the transfer group and consequently the higher rate of TIPS and dialysis, which may be used as a bridge to transplantation. The overall lower rate of liver transplantation in the study groups reflects the high short-term mortality and low availability of organ donors. Despite these available treatment options, the overall prognosis for HRS is still very poor^[1,2]. Therefore, identifying factors that portend poor outcomes is paramount.

From our study results, transfer status is an independent risk factor for mortality and higher hospitalization cost after adjusting for covariates including TIPS and liver transplantation. This could reflect delays in diagnosis or referral and warrants further research. Of note, in our multivariate mortality model, liver transplantation is highly protective of mortality, and TIPS shows a trend towards reducing in-hospital mortality. This is consistent with the known evidence on the efficacy of these procedures^[16,17]. Unsurprisingly, dialysis confers a high mortality risk independent of other factors. Although there is paucity of data on the efficacy of dialysis in HRS, the available evidence is consistent with our study finding that dialysis may be harmful in this population. A study on 102 liver transplant candidates receiving dialysis showed that 32 (31%) survived to transplant and 1-year postoperative mortality was higher in those requiring dialysis before transplant (30% versus 9.7%) compared to those not requiring dialysis. Among those not receiving a transplant, mortality was 94%; and 50% died within 8 days of starting dialysis^[18].

Our study has some limitations. First, the diagnosis of HRS in patients with chronic liver disease is challenging and sometimes difficult to differentiate from acute tubular necrosis and pre-renal azotemia. We used the ICD-9-CM codes that other studies have used for identification and further narrowed their scope by excluding any hospitalizations that included a diagnosis of chronic kidney disease including end stage renal disease. Even though this does not eliminate the bias completely, it makes our population selection stricter than the other studies that have utilized the NIS database.

Second, other factors that can affect patient outcomes such as timing of onset of symptoms, characteristics of referring hospital for the transferred group, and bed-availability in the receiving hospital are not available in this database. Third, we could not ascertain from the database the exact reason for transfer in the transferred group, but we presumed that it is related to HRS diagnosis. Lastly, we could not examine if our estimates are similar in type 1 and type 2 HRS because of the limitations of the ICD-9-CM coding system failing to distinguish between these conditions.

In conclusion, transfer status alone is associated with increased risk of SBP, hepatic coma, mortality, and procedure utilization (TIPS, dialysis, and liver transplantation), and is associated with higher hospitalization cost. Transfer status was not associated with increased length of stay. Future studies are warranted to evaluate the impact of patient-level factors, referring hospital characteristics, and timing of transfer on outcomes in HRS.

Table 5 Multivariate mortality model. Other variables in the model are race, HIV status, and Charlson comorbidity index. UGIB: Upper gastrointestinal bleeding; SBP: Spontaneous s peritonitis; TIPS: Transjugular intrahepatic portosystemic shunt.

	OR (95% CI)	p value
Transferred	1.36 (1.21 - 1.53)	< 0.01
Age	1.01 (1.00 - 1.01)	< 0.01
Hospital Region (reference: North East)		
Midwest	0.59 (0.51 - 0.69)	< 0.01
South	0.83 (0.74 - 0.94)	< 0.01
West	0.93 (0.81 - 1.06)	0.27
Hospital Bed Size (reference: small)		
Medium	1.23 (1.05 - 1.44)	< 0.01
Large	1.17 (1.02 - 1.35)	0.03
Insurance Status (reference: Medicare)		
Medicaid	1.19 (1.04 - 1.35)	< 0.01
Private	1.16 (1.03 - 1.30)	0.01
Uninsured	1.84 (1.55 - 2.19)	< 0.01
Variceal UGIB	1.87 (1.56 - 2.24)	< 0.01
Hepatic Coma	1.34 (1.22 - 1.46)	< 0.01
Spontaneous bacterial peritonitis	1.26 (1.11 - 1.43)	< 0.01
Dialysis	2.39 (1.09 - 2.74)	< 0.01
Liver Transplantation	0.09 (0.06 - 0.13)	< 0.01
TIPS	0.69 (0.44 - 1.07)	0.09

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