Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012

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ABSTRACT

Hepatorenal syndrome (HRS) is one of the leading causes of hospitalizations in patients with chronic liver disease (CLD). We conducted a retrospective national database study to determine the epidemiology of HRS in hospitalized patients with CLD. Data from a Nationwide Inpatient Sample were extracted from 2002 to 2012 using ICD-9-CM codes related to CLD and HRS. The following outcomes were examined: in-hospital mortality, total charges, length of stay (LOS), patient demographics, procedures, complications, and comorbidities. Statistical analysis including regression was performed to examine factors associated with HRS. During 2002–2012, hospital discharges related to CLD increased from 407,246 to 836,475 with an increase of 37.9% for HRS as a complication in this population. Patients with CLD and HRS had worse outcomes compared with patients with CLD without HRS. This was manifested as a higher mortality rate (32.0% vs 10.3%), increased LOS (median 7 vs 5 days), and increased hospital costs (median $16,000 vs $11,000). Logistic regression demonstrated that HIV/AIDS (adjusted OR 2.9, 95% CI 2.2 to 3.9), pneumonia (aOR 2.8, 95% CI 2.3 to 3.2), and esophageal variceal bleeding (aOR 1.9, 95% CI 1.7 to 2.0) were associated with higher mortality in patients with HRS. Conversely, liver transplantation (aOR 0.1, 95% CI 0.1 to 0.1), transjugular intrahepatic portosystemic shunt (aOR 0.5, 95% CI 0.4 to 0.6), and hospitalization in the Midwest region of the USA (aOR 0.7, 95% CI 0.6 to 0.7) were associated with reduced mortality. The incidence of HRS in hospitalized patients with CLD increased during 2002–2012. HRS is associated with significant mortality and morbidity in these patients.

INTRODUCTION

Hepatorenal syndrome (HRS) is a functional form of renal failure that occurs in patients with chronic liver disease (CLD) and histologically normal kidneys. It is due to a decrease in renal perfusion and classically affects patients with cirrhosis and ascites.[1] The prevalence of HRS varies widely in the literature, partly because of differing diagnostic criteria utilized by researchers.[2–4] HRS may be triggered spontaneously or follow a precipitating factor, the most common being spontaneous bacterial peritonitis (SBP).[5] Other less common precipitants include large-volume paracentesis without plasma expansion, gastrointestinal bleeding, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics.

Hospital admissions in the USA related to CLD have been increasing in the past decade.[6] However, the trend of concurrent HRS is currently unknown. Large national databases have been effectively used to study the incidence of complicating factors in patients with CLD.[7 8] We therefore conducted a retrospective analysis using a national US database to study the differences in demographic characteristics, rate of complications, outcomes, and temporal trends in hospitalized patients with CLD with and without HRS.

METHODS

We utilized biennial data (2002–2012) from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) using methods described earlier.[9] Initially, we extracted all entries with any discharge diagnosis of CLD. In the definition of CLD, we included all patients aged 18 years and older with any diagnosis relating to the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: cirrhosis 571, 571.2, 571.5, 571.6; hepatic coma (HC) 572.2; portal hypertension 572.3; other sequelae of CLD 572.8; esophageal varices (EV) 456.0–456.2; ascites 789.5 and SBP 567.23. Among this population of patients with CLD, we next extracted all entries with any ICD-9-CM code discharge diagnosis of HRS: 572.4. Population-based rates relating to hospital discharges were reported per 100,000 population/year.

The outcome variables of interest were in-hospital mortality, total costs (rounded to the nearest $1000), and length of stay (LOS). Demographic details and hospital characteristics were also extracted. Cases were queried for procedures that are well recognized in patients with CLD and HRS. These included ICD-9-CM codes: liver transplantation 50.5, 50.59; renal transplantation 55.6, 55.69; renal dialysis 39.95, 54.98; intra-abdominal venous shunt including transjugular intrahepatic portosystemic shunt (TIPS) 39.1; and paracentesis

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54.91. Comorbid conditions were assessed using the Elixhauser comorbidity index minus the presence of liver disorders and renal failure but including alcohol abuse.[10]

Statistical analyses were performed using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA). To determine the independent association of HRS on outcome variables, we performed case–control matching (HRS vs no HRS). We used high-dimensional propensity scores in a 1:5 matching ratio with a greedy matching algorithm generated by regression analysis of patients with HRS based on demographic details (age, gender), alcohol abuse, SBP, HC, EV bleeding (EVB), and the performance of the aforementioned procedures. The χ^2 tests and the Mann-Whitney U test compared categorical and continuous variables. For trend analysis, we used the Cochrane-Armitage test. To assess demographic parameters, comorbid conditions, and procedures associated with mortality among all inpatients with HRS, univariate and multivariable logistic regression analyses were performed with the presence or absence of mortality as the dichotomous outcome variable. Covariates that were tested for association with mortality in this manner included demographic parameters, procedures, and comorbid conditions that were identified as significant at the univariate level. We tested all between-variable estimated correlation coefficients and determined that multicollinearity was not a problem. ORs, adjusted ORs (aORs), and 95% CIs are reported to identify the strength and significance of mortality and other covariates on the likelihood of an association. The threshold for significance for all analyses was $p<0.01$.

RESULTS

In 2012, there were 836,475 hospital discharges that were related to CLD in patients aged 18 years and older. Within this cohort, HRS was recorded as a diagnosis in 26,985 discharges (3.2%). Table 1 details differences between these two groups of patients with CLD. Patients with and without HRS were of a closely similar median age corresponding to the fifth decade of life (57 years, (IQR 14 vs 59 years, IQR 18 years). Patients with HRS were more likely to be male (65.6% vs 57.4%). Minor differences between the two groups were observed with respect to hospital region, location, teaching status, insurance status, and household income quartile. There was no difference in the number of comorbid conditions (median 4 comorbid conditions in each group).

Patients with HRS suffered a significantly higher rate of alcohol abuse (53.8% vs 37.8%). HRS was also associated with an overall higher incidence of complications. Specifically, patients with HRS demonstrated a higher incidence of HC (43.4% vs 16.0%), SBP (13.3% vs 3.5%), and EVB (10.1% vs 7.4%). Furthermore, patients with HRS underwent a higher frequency of medical and surgical procedures including renal dialysis (20.1% vs 6.4%), liver transplantation (3.7% vs 0.5%), and TIPS (1.3% vs 0.6%). However, the rate of paracentesis was higher in patients without HRS (0.9% vs 0.4%). Patients with HRS who underwent liver transplantation received a simultaneous liver–kidney (SLK) transplant in 20.7% of cases, whereas in patients with CLD without HRS only 4.9% of liver transplants were SLK.

Patients with CLD with HRS demonstrated worse overall outcomes compared to their counterparts without HRS. This manifested in an unadjusted higher mortality rate (32.0% vs 7.0%), lengthier hospital stays (median 7 days (IQR 10 days) vs 4 days (IQR 5 days), and increased hospital costs (median $17,000 (IQR $26,000) vs $9,000 (IQR $12,000)). After adjusting for demographic differences, alcohol abuse, complications, and procedures, HRS in patients with CLD continued to be independently associated with a higher mortality rate (32.0% vs 10.3%), lengthier hospital stays (median 7 days (IQR 10 days) vs 5 days (IQR 6 days)), and increased hospital costs (median $16,000 (IQR $25,000) vs $11,000 (IQR $16,000)) (table 2).

To further investigate the high mortality in patients with CLD with HRS, we performed multivariable regression analysis as described above. The covariates associated with

Table 1 Characteristics of hospitalized patients with chronic liver disease with and without hepatorenal syndrome

Chronic liver disease Population N=836,475	Chronic liver disease without hepatorenal syndrome n=809,490 (96.77%)	Hepatorenal syndrome n=26,985 (3.23%)	p Value
Age (median (IQR))	59 (18)	57 (14)	<0.01
Male (%)	57.4	65.6	<0.01
Died (%)	7	32	<0.01
Length of stay (median (IQR))	4 (5)	7 (10)	<0.01
Hospital costs in US$ (median (IQR))	9,000 (12,000)	17,000 (26,000)	<0.01
Comorbidities (n, (IQR))	4 (2)	4 (2)	NA
Alcohol use (%)	37.8	53.8	<0.01
Spontaneous bacterial peritonitis (%)	3.5	13.3	<0.01
Hepatic coma (%)	16	43.4	<0.01
Liver transplant (%)	0.5	3.7	<0.01
EV bleeding (%)	7.4	10.1	<0.01
TIPS (%)	0.6	1.3	<0.01
Dialysis (%)	6.4	20.1	<0.01
Paracentesis (%)	0.9	0.4	<0.01
SLK transplant	4.9	20.7	<0.01

EV, esophageal varices; NA, not applicable; SLK, simultaneous liver kidney; TIPS, transjugular intrahepatic portosystemic shunt.

Table 2 Deaths, length of stay and cost of hospital stay in patients with chronic liver disease with and without hepatorenal syndrome (HRS) after adjusting for demographic differences, alcohol abuse, complications and procedures

Characteristic	Chronic liver disease without HRS	Chronic liver disease with HRS	OR (95% CI)
Mortality	10.30%	32%	4.1 (4.0 to 4.3)
Length of stay (median, IQR)	5 (6)	7 (10)	p<0.01
Hospital costs US$ (median, IQR)	11 (16)	16 (25)	p<0.01

the greatest risk of mortality in this cohort of patients included the presence of HIV/AIDS (aOR 2.9, 95% CI 2.2 to 3.9), pneumonia (aOR 2.8, 95% CI 2.3 to 3.2), and EVB (aOR 1.9, 95% CI 1.7 to 2.0) (table 3). Liver transplantation was highly protective against mortality (aOR 0.1, 95% CI 0.1 to 0.1) and, to a lesser degree, the performance of TIPS (aOR 0.5, 95% CI 0.4 to 0.6) and hospitalization in the Midwest region of the USA (aOR 0.7, 95% CI 0.6 to 0.7). Notably, the total number of comorbidities, the presence of alcohol abuse, and the location and teaching status of the hospital did not demonstrate a significant association with mortality.

Between the years 2002 and 2012, the number of hospital discharges related to CLD increased from 407,246 to 836,475 (figure 1A). Concurrently, the incidence of HRS in this population increased from 2.3% to 3.2%, representing an overall increase of 37.9% with a significant increased trend.

We also calculated population-adjusted hospitalization rates for discharges related to CLD and HRS (figure 1B). The rate of CLD-related discharges demonstrated an increased trend from 189.7/100,000 population in 2002 to 348.3/100,000 population in 2012. Similarly, an increased trend was observed for HRS-related hospital discharges in the same period of time (4.4/100,000 population in 2002 to 11.2/100,000 population in 2012).

Table 3 Multivariable regression analysis showing effect of covariates on mortality in patients with chronic liver disease with hepatorenal syndrome

Covariates	Adjusted OR (95% CI)
HIV/AIDS	2.9 (2.2 to 3.9)
Pneumonia	2.8 (2.3 to 3.2)
EV bleeding	1.9 (1.7 to 2.0)
SBP	1.5 (1.4 to 1.6)
Hepatic coma	1.4 (1.3 to 1.5)
Liver transplant	0.1 (0.1 to 0.1)
TIPS	0.5 (0.4 to 0.6)
Midwest region	0.7 (0.6 to 0.7)
Cancer	1.6 (1.5 to 1.7)

EV, esophageal varices; SBP, spontaneous bacterial peritonitis; TIPS, transhepatic intrajugular portosystemic shunt.

DISCUSSION

In this study, we studied the occurrence of HRS as a complicating factor in hospitalized patients with CLD with HRS using NIS data and concluded that HRS is associated with worse outcomes overall. Patients with HRS suffered a higher mortality rate, LOS, and hospital costs, which persisted after standardized adjustment for confounding variables. Patients with HRS demonstrated a higher incidence of CLD-related complications including SBP, EVB, and HC. These patients also underwent more frequent medical procedures such as TIPS, renal dialysis, and liver and SLK transplantation. Multivariable regression demonstrated that HIV/AIDS, pneumonia, and EVB were associated with increased mortality in patients with HRS while liver transplantation, TIPS, and admission to a hospital in the Midwest region of the USA were protective in this regard.

Patients with and without HRS demonstrated a similar demographic profile including age, hospital characteristics, and the number of medical comorbidities. The age and gender characteristics of patients with HRS in our study were quite similar to previously reported results obtained from pooled data of over 500 patients.[11] The external validity of our data is high since the NIS derives from a large population-based sample that allows for generalizability to all non-federal hospitals and healthcare settings. Our results indicated a high rate of alcohol abuse in patients with CLD with HRS.[12] Alcohol-related cirrhosis is a leading risk factor for HRS accounting for the majority of these cases.[2 11] However, stratified analysis for other causes of cirrhosis was not attempted as part of our analysis.

The high mortality in patients with HRS observed in our study highlights the fact that HRS is a disease associated with significant morbidity and high mortality in patients with CLD with an average median survival time of approximately 3 months.[13–16] Patients with CLD with HRS were four times at higher risk for death compared to their matched counterparts without HRS. Patients with CLD with HRS also incurred lengthier hospital stays and significantly higher hospital costs in this respect. Intensive care and procedural costs were likely a major contributor to the higher costs; patients with CLD with HRS underwent a median of three procedures (IQR 5) during their hospital stay compared to a median of two procedures (IQR 3) for patients with CLD without HRS (p<0.01; data not shown).

We observed a high incidence of SBP, EVB, and HC in patients with HRS. Given the constraints of the NIS database, a temporal relationship could not be established between these conditions and HRS, although it has been previously demonstrated that SBP and EVB precede HRS.[5] Specifically, SBP is the most common precipitating factor in the development of HRS.[17 18] SBP may induce HRS by one of two pathways, either by the release of cytokines and endotoxins causing increased production of vasodilator substances and/or by sepsis-induced cardiomyopathy resulting in reduced cardiac output.[5 19] Gastrointestinal bleeding is another well-recognized risk factor for HRS through the precipitation of a systemic inflammatory response with the release of pro-inflammatory cytokines.[20] Regression analysis of our data demonstrated that EVB was independently associated with a higher mortality in the HRS group.

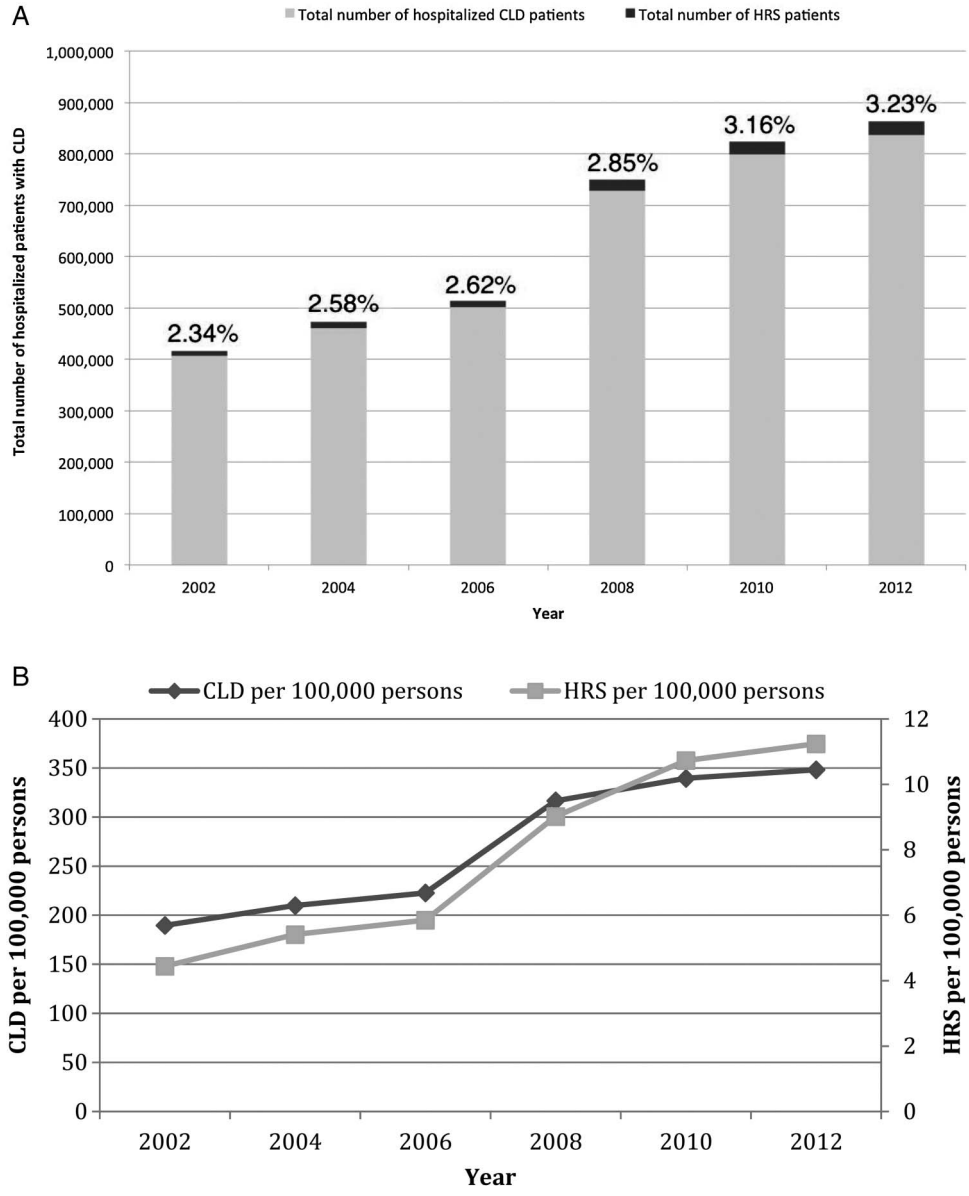

Figure 1 Increasing trend of hospitalizations of patients with chronic liver disease (CLD) with concurrent increased incidence of patients with hepatorenal syndrome (HRS) during 2002–2012. (A) The total number of hospitalized patients. Percentages in red represent HRS complicating cases of CLD. (B) Population-adjusted hospitalization rates for discharges related to CLD and HRS using US Census data for each listed year.

Conversely, the relationship between HC and HRS has not been well studied. HC is a known complication of CLD and is present to various degrees of severity in hospitalized patients with CLD.[21] Once again, the constraints of the NIS database did not enable the establishment of a temporal relationship between the onset of HC and HRS. Therefore, it was not possible to determine if HC was a precipitating factor for HRS or merely the reflection of a greater degree of clinical deterioration in these patients. It is notable that HC in itself has been shown to be an independent predictor of liver-related death (OR=2.3, p=0.082).[22] Finally, while large volume paracentesis (LVP) without plasma expansion has been previously noted to be an important precipitating factor for HRS,[23] paracentesis was recorded in just 0.4% of our study cohort. It is possible that with the heightened awareness among physicians regarding this risk, the majority of patients received concurrent albumin infusion with LVP.

A substantial number of patients with HRS underwent renal dialysis. The indication for this may have been complications of renal failure such as metabolic acidosis, hyperkalemia, hypervolemia, and uremic symptoms. Using ICD-9-CM codes, we were not able to differentiate continuous veno-venous hemofiltration, which is the preferred modality in HRS, from hemodialysis. Also, it was not possible to identify individual factors leading to renal dialysis in this group of patients. Nonetheless, untreated HRS can rapidly progress to a need for renal replacement therapy,[24] which was evidenced by the high rate of renal dialysis in our study cohort.

The outcome of patients with HRS, as well as recovery of kidney function, is strongly dependent on reversal of the hepatic failure, whether this is spontaneous following medical therapy, or resulting from successful liver transplantation.[25] In our study, liver transplantation occurred in approximately 4% of the cohort with SLK accounting for approximately one-fifth of all cases. The 5-year survival for HRS has been noted to be 60% for patients who underwent liver transplantation compared with 0% for patients who did not.[26]

While the TIPS procedure may be useful in type 2 HRS and refractory ascites, the majority of patients are ineligible due to the presence of various contraindications to the procedure including an international normalized ratio >2, serum bilirubin >5 mg/dL, Child Pugh score >11, and cardiopulmonary disease.[27] The efficacy of TIPS in the treatment of type 1 HRS has been evaluated only in a few pilot or retrospective studies, with survival rates at 1 and 3 months within 50–71% and 28–64%, respectively. [28–30]

In their single-center retrospective cohort study, Heidemann *et al*[31] identified age, alcohol abuse, duration of medical therapy, and the model in end-stage liver disease (MELD) score as independent predictors of survival in patients with HRS. The MELD score is the major determinant of mortality in patients with HRS;[15 32] unfortunately, the absence of laboratory data in the NIS precluded us from assessing for this. However, we did identify several other unique demographic features and comorbidities as independent risk factors for mortality in patients with HRS such as the presence of HIV/AIDS. While liver transplantation was the greatest protective factor against mortality, our data suggested that patients who were hospitalized in the Midwest region of the USA also had a lower mortality. This geographic variation is similar to data described by Mellinger *et al*,[33] who reported that patients with cirrhosis in the Midwest had the lowest risk of inpatient mortality (OR 0.54; p<0.001).

To the best of our knowledge, there are no previous large-scale data regarding the temporal trends of HRS in relation to CLD in the USA. Our data demonstrated an increase in the rates of discharge for patients with both CLD and HRS during the decade 2002–2012. However, it may be more meaningful to state that there was a contemporaneous increase in the incidence of HRS as a complicating condition in hospitalized patients with CLD. The reasons for this are unknown; they could be possibly related to a revision of the criteria defining HRS.[34] The strengths of our study include a large number of patients and the mitigation of regional and institutional biases since the data were derived from a population-based sample. This allows for a more balanced estimation of clinical outcomes by accounting for multiple confounders.

There are limitations to our study. First, we relied exclusively on ICD-9-CM codes for case identification. Discharge diagnoses with acute kidney injury or renal impairment in those with CLD were not studied. Second, there was a lack of data pertaining to MELD score calculations, medication, antibiotic usage, and disease severity. Third, the NIS database does not enable distinguishing individual patients with repeat admissions. In addition, the NIS does not include patients in the Veterans Administration hospitals. This could have led to an underestimation of overall national burden for CLD and HRS since there is a high prevalence of hepatitis C virus and alcohol-related liver disease within the Veterans Administration population.[33 35] Finally, our results represent a weighted estimate of national data.

In conclusion, there was an increased incidence of HRS in hospitalized patients with CLD from 2002 to 2012. This was associated with increased inpatient mortality, greater LOS, and higher hospital costs. Patients with HRS were more likely to abuse alcohol and develop medical complications. While liver transplantation was highly protective against mortality in patients with HRS, HIV/AIDS was an independent risk factor for the same. Our study serves to better understand the epidemiology of HRS in patients with CLD. Further external validation of our results and analysis of current epidemiological trends will be invaluable in managing this difficult condition.

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Contributions CP participated in the research design, writing of the article, and data analysis and interpretation. MO participated in the research design and writing of the article. AD, MD, BSJ, RG, PP, and RT participated in data interpretation and writing of the article.

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REFERENCES

1 Low G, Alexander GJ, Lomas DJ. Hepatorenal syndrome: aetiology, diagnosis, and treatment. *Gastroenterol Res Pract* 2015;2015:207012.
2 Salerno F, Cazzaniga M, Merli M, *et al*. Diagnosis, treatment and survival of patients with hepatorenal syndrome: a survey on daily medical practice. *J Hepatol* 2011;55:1241–8.
3 Martin-Llahi M, Guevara M, Torre A, *et al*. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011;140:488–96.e4.
4 Thabut D, Massard J, Gangloff A, *et al*. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology* 2007;46:1872–82.
5 Wadei HM, Mai ML, Ahsan N, *et al*. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol* 2006;1:1066–79.
6 Pant C, Desai M, Deshpande A, *et al*. Esophageal variceal bleeding in hospitalized patients with cirrhosis. *J Hosp Med* 2015;10:453–6.
7 Jamal MM, Samarasena JB, Hashemzadeh M, *et al*. Declining hospitalization rate of esophageal variceal bleeding in the United States. *Clin Gastroenterol Hepatol* 2008;6:689–95; quiz 05.
8 Singal AK, Salameh H, Kamath PS. Prevalence and in-hospital mortality trends of infections among patients with cirrhosis: a nationwide study of hospitalised patients in the United States. *Aliment Pharmacol Ther* 2014;40:105–12.
9 Pant C, Anderson MP, O'Connor JA, *et al*. Association of Clostridium difficile infection with outcomes of hospitalized solid organ transplant recipients: results from the 2009 Nationwide Inpatient Sample database. *Transpl Infect Dis* 2012;14:540–7.
10 Elixhauser A, Steiner C, Harris DR, *et al*. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
11 Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology* 2008;48:2064–77.
12 Younossi ZM, Stepanova M, Afendy M, *et al*. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 2011;9:524–30.e1; quiz e60. Epub 2011/03/29.
13 Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009;361:1279–90.
14 Gines A, Escorsell A, Gines P, *et al*. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* 1993;105:229–36.

15 Alessandria C, Ozdogan O, Guevara M, *et al*. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 2005;41:1282–9.
16 Schepke M, Appenrodt B, Heller J, *et al*. Prognostic factors for patients with cirrhosis and kidney dysfunction in the era of MELD: results of a prospective study. *Liver Int* 2006;26:834–9.
17 Follo A, Llovet JM, Navasa M, *et al*. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495–501.
18 Sort P, Navasa M, Arroyo V, *et al*. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403–9.
19 Navasa M, Follo A, Filella X, *et al*. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;27:1227–32.
20 Cardenas A, Gines P, Uriz J, *et al*. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology* 2001;34(4 Pt 1):671–6.
21 Aldridge DR, Tranah EJ, Shawcross DL. Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. *J Clin Exp Hepatol* 2015;5(Suppl 1):S7–20.
22 Wedd J, Bambha KM, Stotts M, *et al*. Stage of cirrhosis predicts the risk of liver-related death in patients with low Model for End-Stage Liver Disease scores and cirrhosis awaiting liver transplantation. *Liver Transpl* 2014;20:1193–201.
23 Gines P, Tito L, Arroyo V, *et al*. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988;94:1493–502.
24 Dundar HZ, Yilmazlar T. Management of hepatorenal syndrome. *World J Nephrol* 2015;4:277–86.
25 Cassinello C, Moreno E, Gozalo A, *et al*. Effects of orthotopic liver transplantation on vasoactive systems and renal function in patients with advanced liver cirrhosis. *Dig Dis Sci* 2003;48:179–86.
26 Gonwa TA, Klintmalm GB, Levy M, *et al*. Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995;59:361–5.
27 Patidar KR, Sydnor M, Sanyal AJ. Transjugular intrahepatic portosystemic shunt. *Clin Liver Dis* 2014;18:853–76.
28 Appenrodt B, Zielinski J, Brensing KA, *et al*. Degree of hepatic dysfunction and improvement of renal function predict survival in patients with HRS type I: a retrospective analysis. *Eur J Gastroenterol Hepatol* 2009;21:1428–32.
29 Guevara M, Gines P, Bandi JC, *et al*. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998;28:416–22.
30 Brensing KA, Textor J, Perz J, *et al*. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *GUT* 2000;47:288–95.
31 Heidemann J, Bartels C, Berssenbrugge C, *et al*. Hepatorenal syndrome: outcome of response to therapy and predictors of survival. *Gastroenterol Res Pract* 2015;2015:457613.
32 Kamath PS, Kim WR. Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology* 2007;45:797–805.
33 Mellinger JL, Richardson CR, Mathur AK, *et al*. Variation among United States hospitals in inpatient mortality for cirrhosis. *Clin Gastroenterol Hepatol* 2015;13:577–84.
34 Lenz K, Buder R, Kapun L, *et al*. Treatment and management of ascites and hepatorenal syndrome: an update. *Therap Adv Gastroenterol* 2015;8:83–100.
35 Mansell D, Penk W, Hankin CS, *et al*. The illness burden of alcohol-related disorders among VA patients: the Veterans Health Study. *J Ambul Care Manage* 2006;29:61–70.