

COMPLICATIONS OF CIRRHOSIS: STRATEGIES TO IMPROVE LONG-TERM PATIENT OUTCOMES

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Educational Objectives

- Recognize the signs of complications due to cirrhosis and the importance of early intervention.
- Describe evolving patient management strategies for hepatic encephalopathy in the hospital/outpatient setting.
- Apply the latest patient management strategies in order to decrease hospital readmissions due to hepatic encephalopathy.

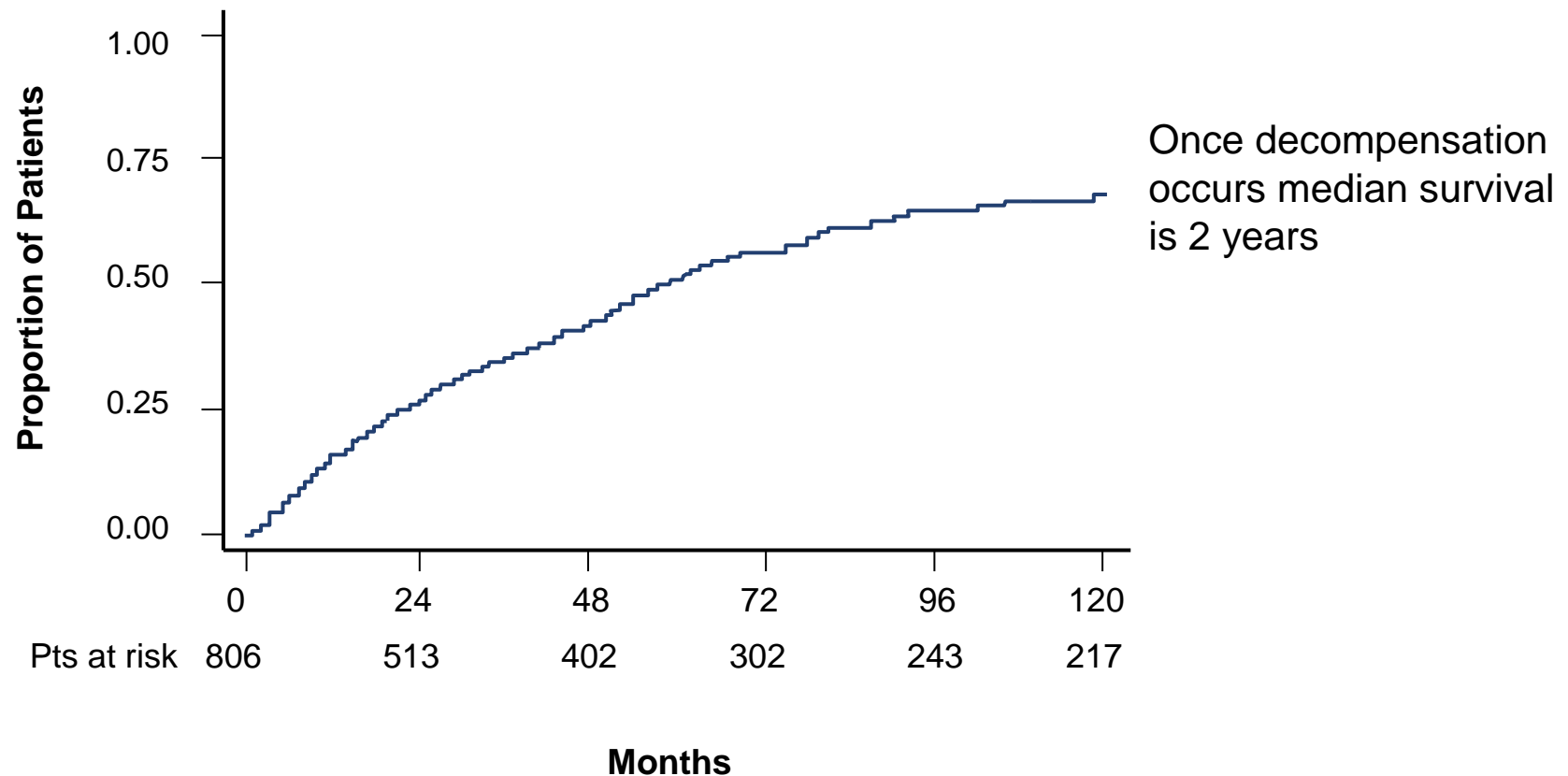
Prevalence of Cirrhosis

- The prevalence of cirrhosis, both worldwide and in the US, is unknown
 - Compensated cirrhosis often goes undetected for prolonged periods of time
- Experts estimate that up to 1% of the population (~3 million) may have histological cirrhosis

Compensated Cirrhosis May Be Difficult to Recognize

- Asymptomatic
 - Subtle clues may be overlooked
 - Thrombocytopenia
 - Muscle wasting
 - AST>ALT without alcohol consumption
 - Liver enzymes may not be abnormal
 - Etiology may be remote
 - Prior alcohol use
 - Uncontrolled diabetes mellitus and obesity

Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Stage Over Time



Decompensated Cirrhosis

- Primary complications include:
 - Hepatic encephalopathy
 - Ascites
 - Variceal hemorrhage
- Other possible complications include:
 - Spontaneous bacterial peritonitis
 - Hepatic hydrothorax
 - Hepatorenal syndrome
 - Portopulmonary hypertension
 - Hepatocellular carcinoma
 - Portal vein thrombosis

Topics

- **Hepatic Encephalopathy**
- Economic and Social Burden
- Hospital Readmissions
- Cognitive Impairment

Treatment Goals for Overt HE

- Provision for supportive care
- Identification and removal of precipitating factors
 - Infection, GI bleed, dehydration
- Reduction of nitrogenous load from gut
- Correction of electrolyte abnormalities
- Long-term therapy assessment
 - Control of potential precipitating factors
 - Higher likelihood of recurrent encephalopathy
 - Assessment of need for liver transplantation

Current Therapy Options for HE

Drug Name	Drug Class	Indication
Lactulose	Poorly absorbed disaccharide	<ul style="list-style-type: none">• Decrease blood ammonia concentration• Prevention and treatment of portal-systemic encephalopathy
Rifaximin	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.
Neomycin	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin	Aminoglycoside antibiotic	Not approved for HE

Lactulose

- Currently the mainstay of therapy of HE; ~70% to 80% of patients with acute and chronic HE improve with lactulose treatment
- Mechanism of action:
 - A non-absorbable disaccharide that is fermented in the colon
 - Metabolism by the bacterial flora in the colon to lactic acid lowers the colonic pH
 - Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume

Lactulose (Cont.)

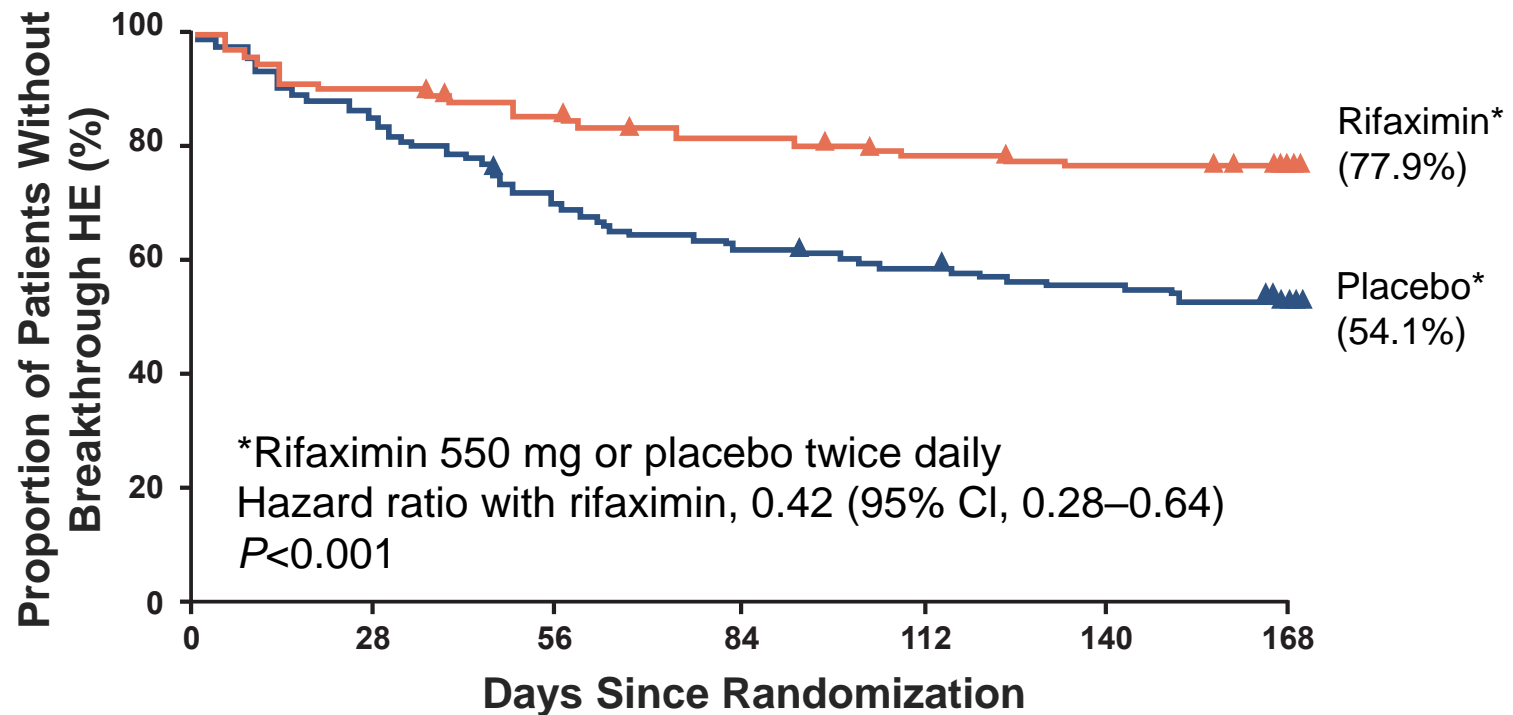
- Administered orally, by mouth or through a nasogastric tube or via retention enemas
- Dose: 45 to 90 g/day, titrated to achieve 2 to 3 soft stools per day with a pH below 6
- Principal side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence
- Systematic review of clinical studies found insufficient evidence to support or refute the use of lactulose for HE

Rifaximin

- Minimally absorbed (<0.4%) oral antibiotic
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria
- No clinical drug interactions reported
- No dosing adjustment required in patients with liver disease or renal insufficiency
- Approved for overt recurrent HE risk reduction in patients ≥ 18 years of age

Rifaximin Trial: Time to First Breakthrough HE Episode Primary Endpoint

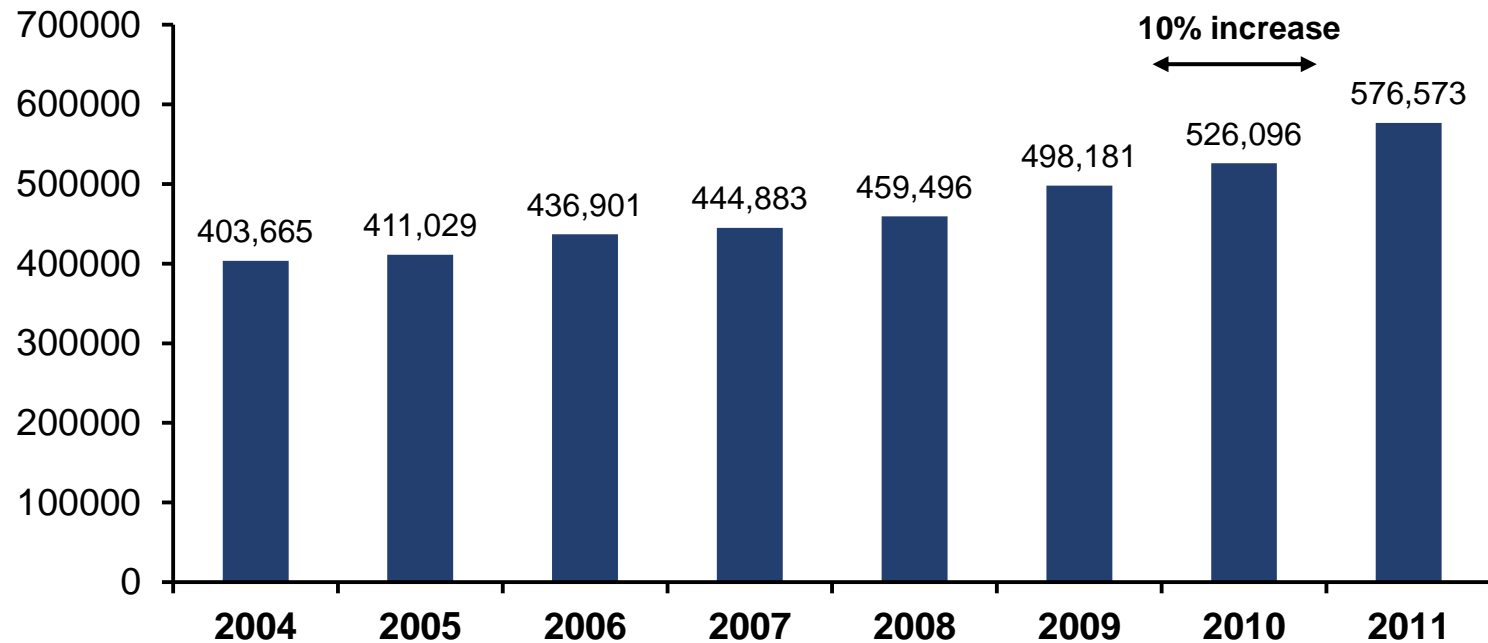
- 91% of patients in both arms received concomitant lactulose



Topics

- Hepatic Encephalopathy
- Economic and Social Burden
- Hospital Readmissions
- Cognitive Impairment

US Hospital Discharges Due to Cirrhosis Are Increasing



*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.

HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD.

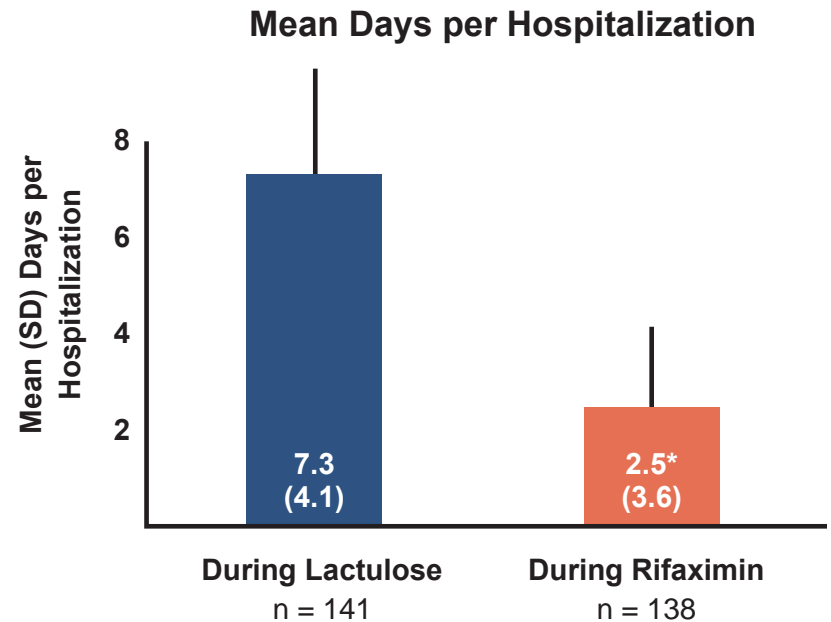
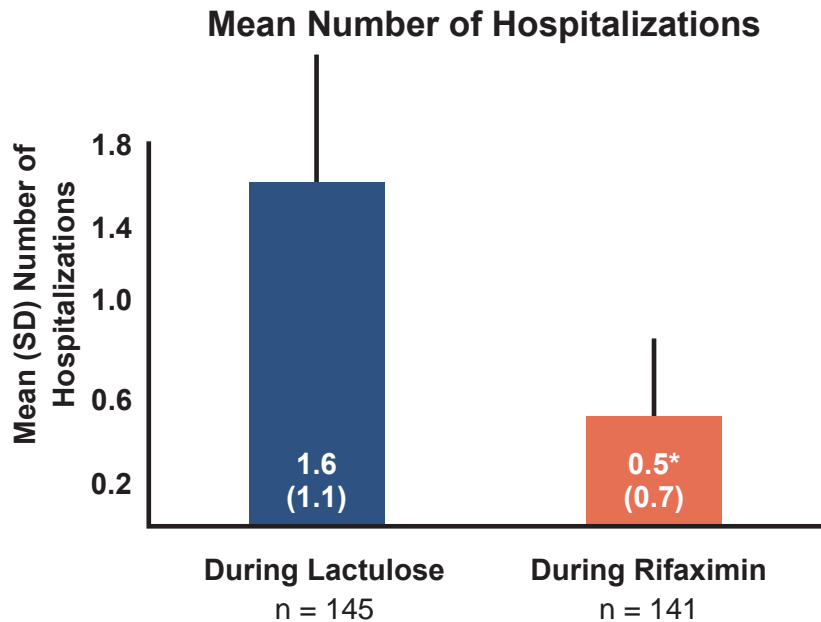
<http://hcupnet.ahrq.gov>. Accessed January 2014.

Resource Utilization for Patients Hospitalized with Hepatic Encephalopathy, 2005-2009

Increase health care utilization in patients discharged with the diagnosis of hepatic encephalopathy

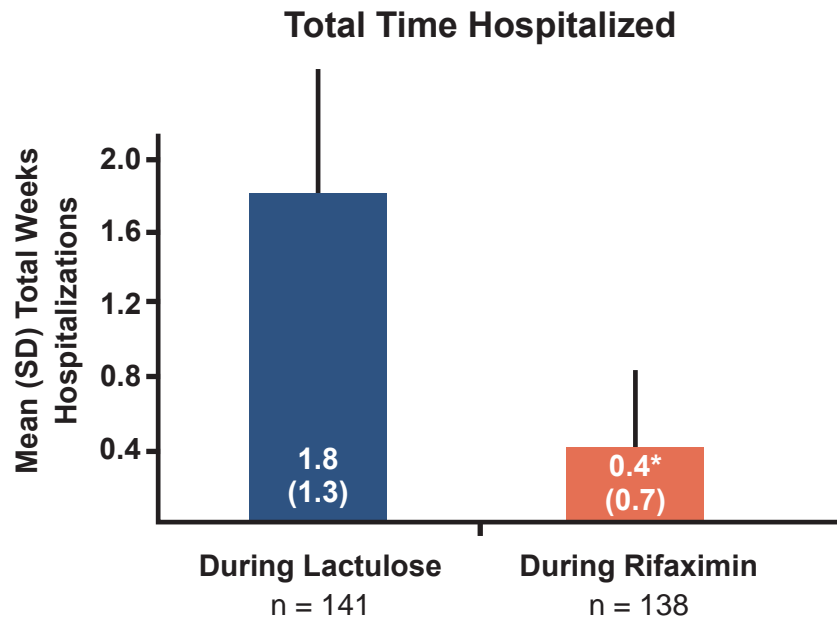
Parameter	2005	2006	2007	2008	2009	P
Number of procedures	1.91 ± 0.06	1.92 ± 0.05	2.10 ± 0.07	2.20 ± 0.07	2.24 ± 0.06	<.0001
Length of stay, d	8.04 ± 0.17	7.95 ± 0.11	7.98 ± 0.11	8.40 ± 0.18	8.53 ± 0.17	.0191
Average charge (2009 \$)	46,663 ± 2180	47,297 ± 1728	51,889 ± 2308	59,786 ± 3546	63,107 ± 3244	<.0001
Average cost (2009 \$)	16,512 ± 709	15,851 ± 449	16,588 ± 615	17,832 ± 762	17,812 ± 764	.1697
Total national charge, (2009 \$) millions	4676.7	5059.5	5603.5	6484.0	7244.7	
Total national cost, (2009 \$) millions	1651.1	1695.6	1791.3	1932.0	2044.5	

Frequency and Duration of Hospitalization During the Lactulose and Rifaximin Period in Patients with Hepatic Encephalopathy

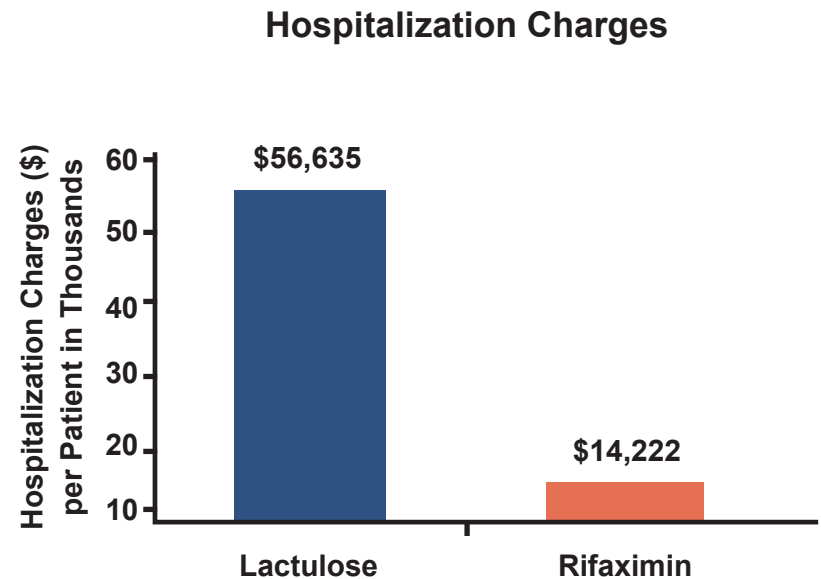


* $P < 0.001$ rifaximin period versus lactulose period, paired t -test
Leevy CB, Phillips JA. *Dig Dis Sci*. 2006.

Total Time Hospitalized and Charges During the Lactulose and Rifaximin Period in Patients with Hepatic Encephalopathy



* $P < 0.001$ rifaximin period versus lactulose period, paired t -test



*Charges were calculated in 2005 dollars based on average cost per hospital day as determined by the 2003 Healthcare Cost Utilization Project for ICD-9-CM principal diagnosis code 572.2. A healthcare cost index was used to predict 2004 and 2005 costs.

Demographic and Hospitalization Information for Both Groups

	Gender (male/female)	MELD (average)	Age (mean) (years)	Hospitalizations (total)
Group one (lactulose)	18/6	14 (range 10-19)	48	19
Group two (rifaximin)	10/5	15 (range 10-18)	47	3

Notes: Hospitalization number and treatment cost in patients with hepatic encephalopathy who received lactulose or rifaximin therapy. Treatment with rifaximin therapy reduced the number of hospitalizations compared with treatment with lactulose therapy concurrent with a reduction in total cost of therapy per patient (2005 US dollars).

Abbreviation: MELD, Model for End-Stage Liver Disease.

Neff GW, et al. *Clinicoecon Outcomes Res.* 2013.

Therapy received affected hospital stays and costs in patients with OHE

Group (outpatient therapy → added hospital therapy)	n	MELD score (mean)	Length of stay (days)	Time to start of full diet (days)	HCUP (7,500/d)	Insured/MC/MD costs (8,382/d)
(1) Lac→Lac	18	11.5	5.75	4.1	43,125	48,197
(2) RFX→Lac	19	12.5	3.4	2.25	25,500	28,329
(3) Lac→RFX	20	10.5	4.25	3.5	31,875	35,624
(4) NT→Lac/RFX	14	11.5	5.25	3.8	39,375	44,006
(5) NT→Lac	28	13	6.5	4.5	48,750	54,483

Notes: There were five groups of patients with three admission treatments: no treatment, lactulose, or rifaximin. Patients were then treated with lactulose, rifaximin, or both. The most expensive group in terms of length of stay and overall costs were the no-treatment groups. The least expensive in terms of length of stay and overall costs was the group presenting on rifaximin therapy.

Abbreviation: d, day; HCUP, Healthcare Cost and Utilization Project; Lac, lactulose; Lac/RFX, lactulose and rifaximin combination therapy; MC, Medicare; MD, Medicaid; MELD, Model for End-Stage Liver Disease; NT, no treatment; OHE, overt hepatic encephalopathy; RFX, rifaximin monotherapy.

Neff GW, et al. *Clinicoecon Outcomes Res.* 2013.

Impact of Affordable Care Act (ACA) on Patients with Hepatic Encephalopathy

- Under the ACA, the Centers for Medicare & Medicaid Services (CMS) assign penalties to hospitals for underperformance in certain conditions
- In an effort to decrease costs and improve quality of care, CMS has selected certain core conditions to measure and evaluate

Measures

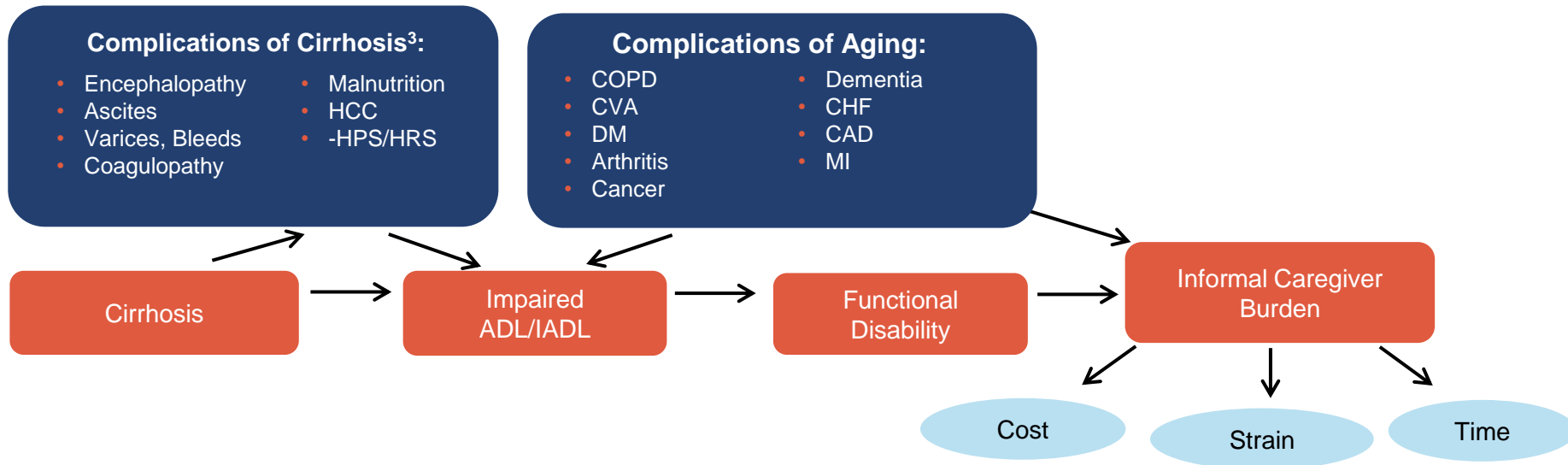
- 30-day readmission rates
- Average length of stay
- Mortality

Care Measure Conditions	Hospital-Acquired Conditions
<ul style="list-style-type: none"> • Acute myocardial infarction (AMI) 	<ul style="list-style-type: none"> • Central-line associated blood stream infection (CLA-BSI) • Methicillin-resistant <i>staphylococcus aureas</i> (MRSA)
<ul style="list-style-type: none"> • Heart failure (HF) 	<ul style="list-style-type: none"> • Catheter-associated urinary tract infection (CA-UAT) • <i>Clostridium difficile</i> (C. diff)
<ul style="list-style-type: none"> • Chronic obstructive pulmonary disorder (COPD) 	<ul style="list-style-type: none"> • Sepsis • Falls
<ul style="list-style-type: none"> • Pneumonia 	<ul style="list-style-type: none"> • Pressure ulcers

- While the ACA does not currently include regulations for HE, in a retrospective review of 21 million inpatient admissions in 2014, 42% of patients admitted with HE presented with a core measure comorbidity.

HE Disrupts Caregiver's Lives

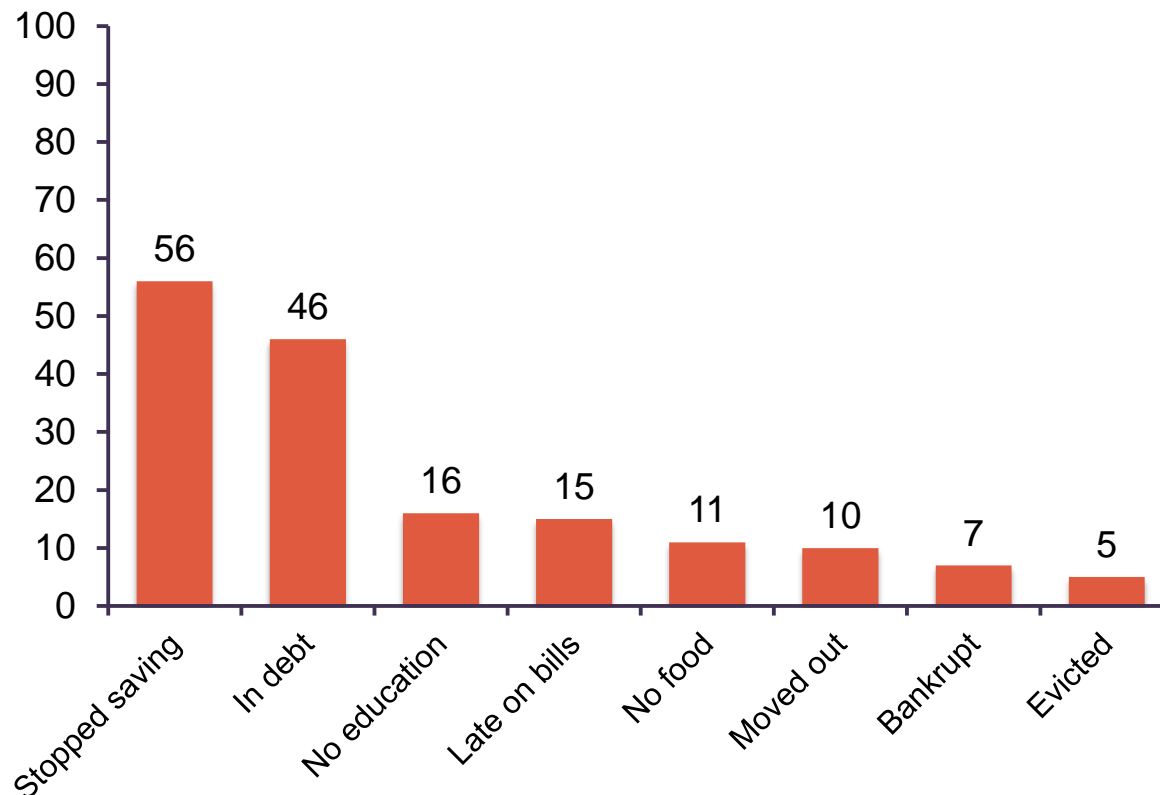
- Overt episodes of HE are debilitating, can render the patient incapable of self-care¹
- HE caregivers report greater disruptions compared to cirrhosis caregivers²



ADL, activities of daily living; IADL, instrumental activities of daily living; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GI, gastrointestinal; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; MI, myocardial infarction
1. Bass, et al. *N Engl J Med.* 2010; 2. Rakoski, et al. *Hepatology.* 2012; 3. Bajaj, et al. *Am J Gastroenterol.* 2011.

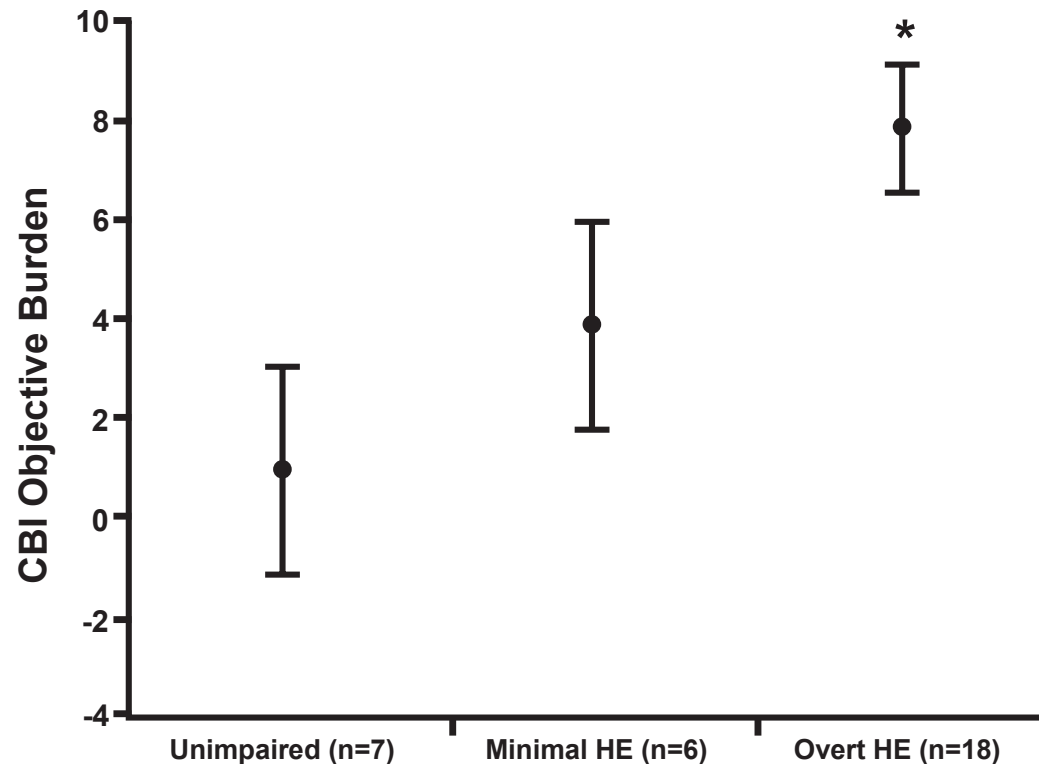
Impact of Hepatic Encephalopathy on Affected Family Within the Last Three Years

Hepatic encephalopathy impacts family daily functioning compared to previous three years of patient diagnosis

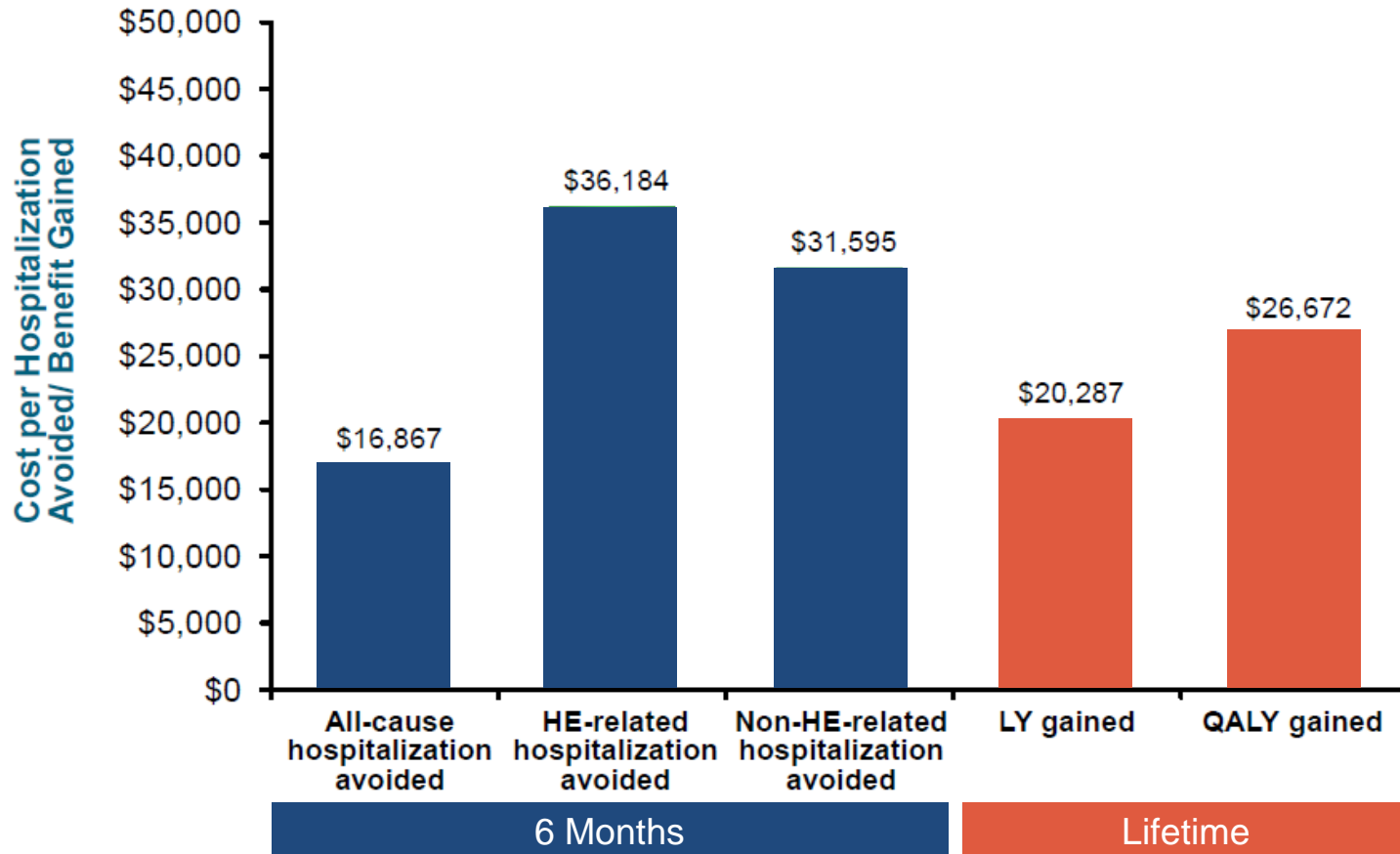


Hepatic Encephalopathy Impact on Caregivers

Increase caregiver burden with increasing severity of hepatic encephalopathy
Mean (\pm SE) caregivers' scores in the 'objective burden' domain of the Caregiver Burden Inventory (CBI)



Incremental Cost-Effectiveness Ratios



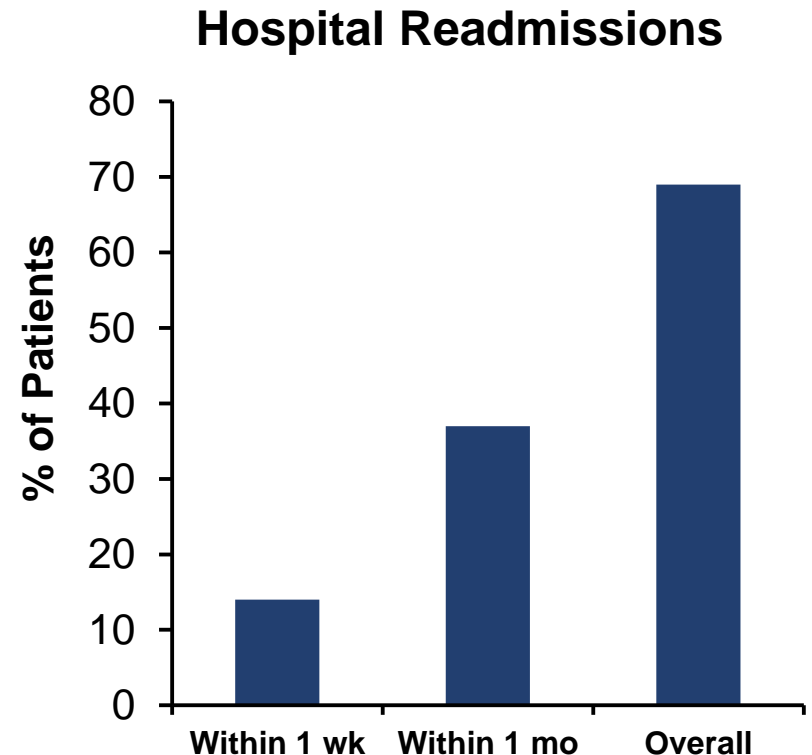
Key: HE – hepatic encephalopathy; LY – life-year; QALY – quality-adjusted life-year.

Topics

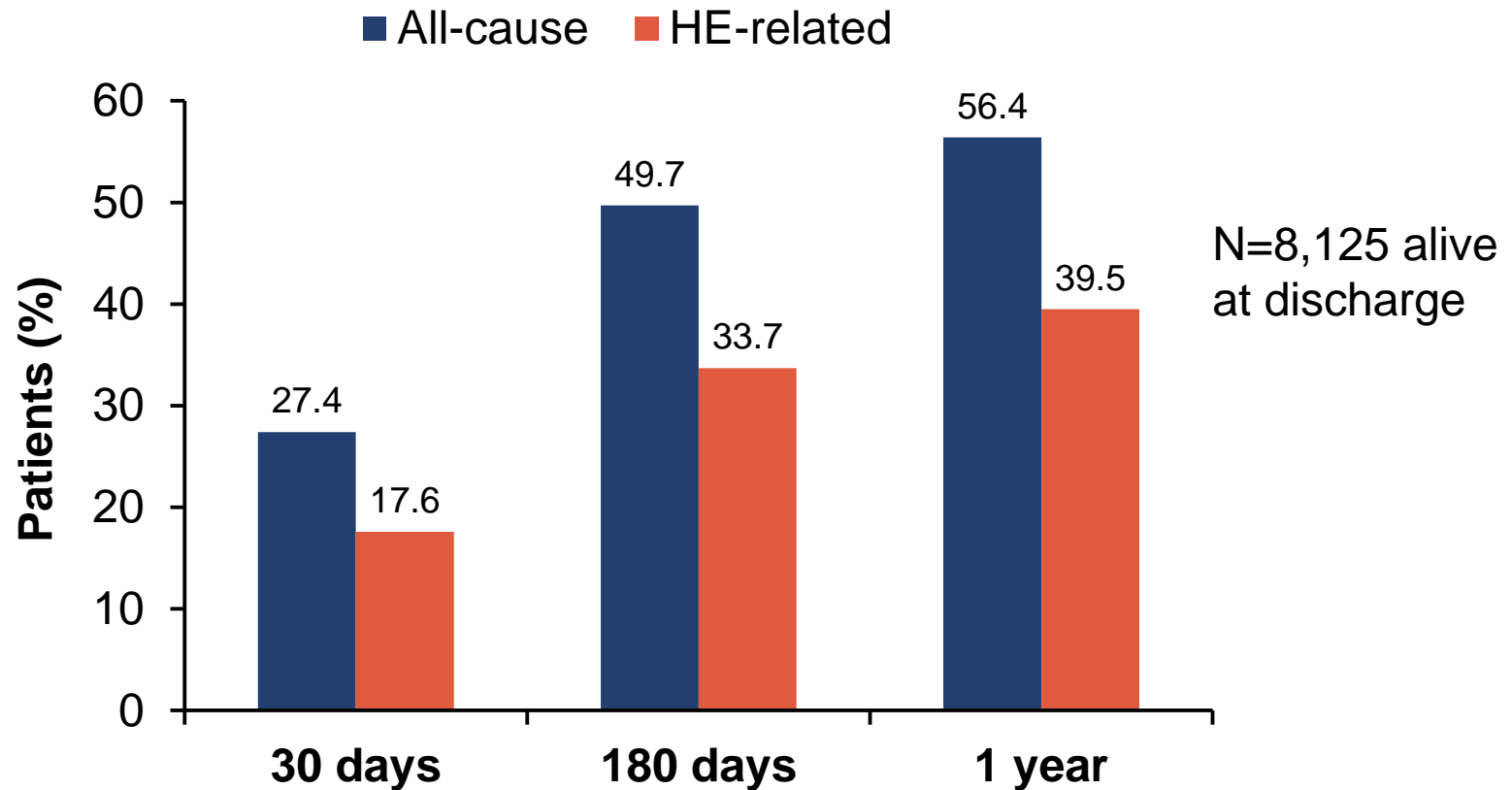
- Hepatic Encephalopathy
- Economic and Social Burden
- Hospital Readmissions
- Cognitive Impairment

Hospital Readmissions Among Patients with Decompensated Cirrhosis are Common

- Retrospective study of 402 patients from an academic transplant center
- Follow-up time censored at death, elective admissions such as transplant or post-procedure observation, or the date of last clinic note; median follow-up was 203 days
- Included cirrhotic patients hospitalized for ascites, SBP, renal failure, hepatic encephalopathy, or variceal hemorrhage
- Median time to readmission was 67 days
- Median number of readmissions was 2 (range 0-40); overall rate was 3 hospitalizations/person-year



All-Cause and HE-Related Re-Hospitalization for Patients with Hepatic Encephalopathy



Unadjusted and Adjusted Odds Ratios for 30-Day Readmissions by Condition for Complications of Liver Disease

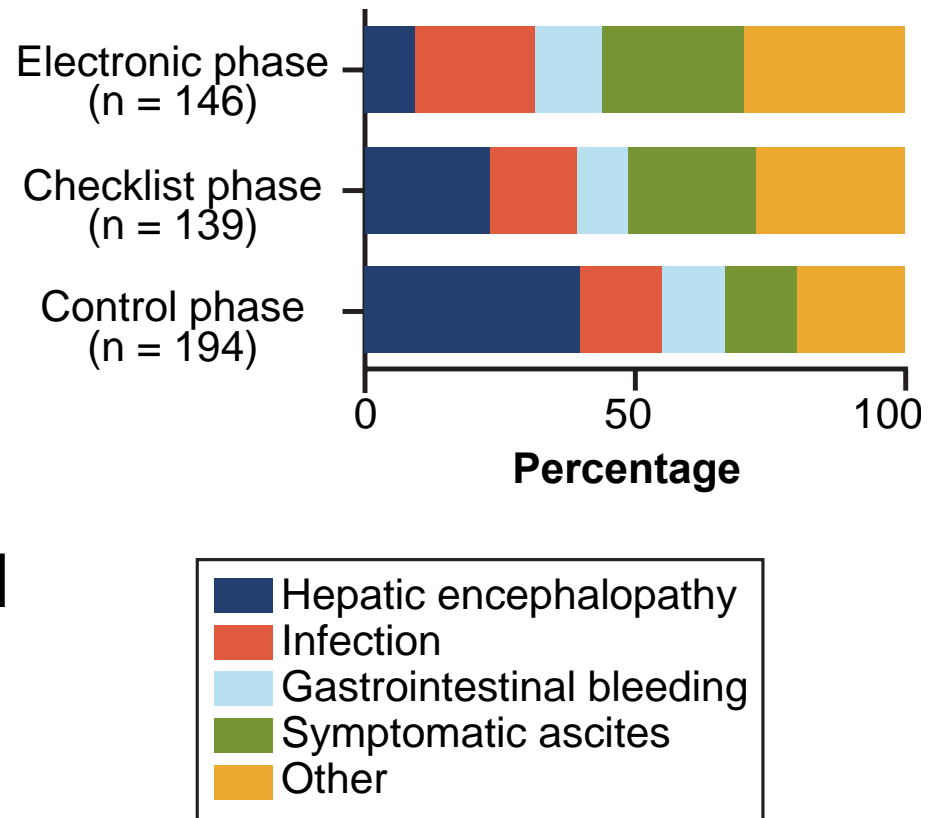
	30-Day Hepatology Readmission		
	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Number of complications			
1 vs 0	1.58 (1.47-1.71)	1.74 (1.61-1.88)	
2 vs 0	4.20 (3.81-4.62)	4.31 (3.91-4.75)	
3+ vs 0	5.42 (4.61-6.37)	5.73 (4.86-6.76)	
Type of complication			
Ascites	1.28 (1.20-1.37)	1.47 (1.37-1.58)	1.78 (1.66-1.90)
Variceal hemorrhage	1.85 (1.71-2.00)	1.69 (1.56-1.83)	1.55 (1.43-1.69)
Hepatic encephalopathy	2.62 (2.41-2.83)	2.67 (2.46-2.89)	3.23 (2.97-3.52)
Hepatorenal syndrome	2.33 (1.90-2.85)	2.46 (2.00-3.02)	1.41 (1.13-1.77)
Hepatocellular carcinoma	1.79 (1.61-2.00)	1.64 (1.45-1.84)	1.70 (1.51-1.91)
Other specified conditions			
Alcoholic liver disease	1.27 (1.19-1.35)	1.19 (1.11-1.28)	1.11 (1.03-1.19)
Hepatitis C	1.85 (1.72-1.98)	1.68 (1.57-1.80)	2.05 (1.91-2.21)
Hepatitis B	1.46 (1.25-1.70)	1.30 (1.12-1.52)	1.43 (1.22-1.67)
Acute kidney injury	1.28 (1.18-1.38)	1.48 (1.36-1.62)	1.31 (1.19-1.43)
Infection	0.96 (0.90-1.02)	1.05 (0.98-1.13)	1.02 (0.95-1.10)

Unadjusted and Adjusted Odds Ratios for 90-Day Readmissions by Condition for Complications of Liver Disease

	30-Day Hepatology Readmission		
	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Number of complications			
1 vs 0	1.44 (1.35-1.53)	1.62 (1.52-1.73)	
2 vs 0	3.83 (3.54-4.14)	4.03 (3.71-4.37)	
3+ vs 0	4.70 (4.11-5.37)	5.22 (4.55-6.00)	
Type of complication			
Ascites	1.11 (1.05-1.18)	1.31 (1.23-1.39)	1.60 (1.52-1.69)
Variceal hemorrhage	2.03 (1.90-2.16)	1.83 (1.71-1.95)	1.70 (1.60-1.82)
Hepatic encephalopathy	2.44 (2.28-2.60)	2.53 (2.37-2.70)	3.07 (2.86-3.30)
Hepatorenal syndrome	2.06 (1.75-2.43)	2.31 (1.96-2.73)	1.43 (1.20-1.71)
Hepatocellular carcinoma	1.98 (1.82-2.15)	1.79 (1.63-1.96)	1.83 (1.67-2.01)
Other specified conditions			
Alcoholic liver disease	1.27 (1.21-1.33)	1.17 (1.11-1.24)	1.10 (1.04-1.16)
Hepatitis C	1.97 (1.87-2.09)	1.78 (1.69-1.88)	2.09 (1.97-2.22)
Hepatitis B	1.48 (1.30-1.68)	1.32 (1.16-1.51)	1.41 (1.23-1.61)
Acute kidney injury	1.12 (1.05-1.20)	1.37 (1.28-1.47)	1.23 (1.15-1.32)
Infection	0.89 (0.85-0.94)	1.03 (0.98-1.09)	1.02 (0.96-1.08)

Reducing 30 Day Readmission by Intervention Phase

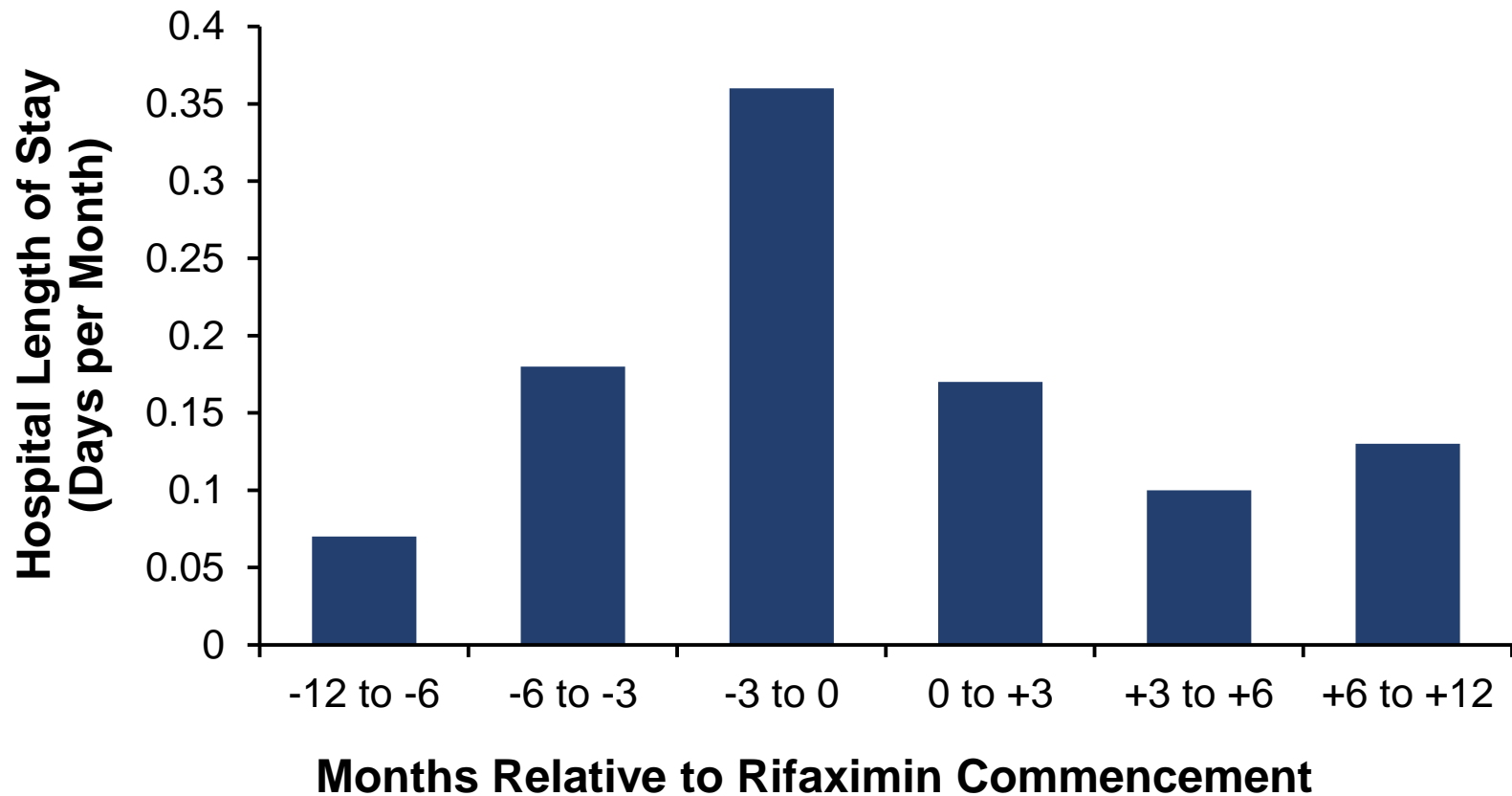
- Electronic phase ~ Checklist items incorporated into electronic provider order system
- Check list phase ~ QI checklist prompted medication review and dosing



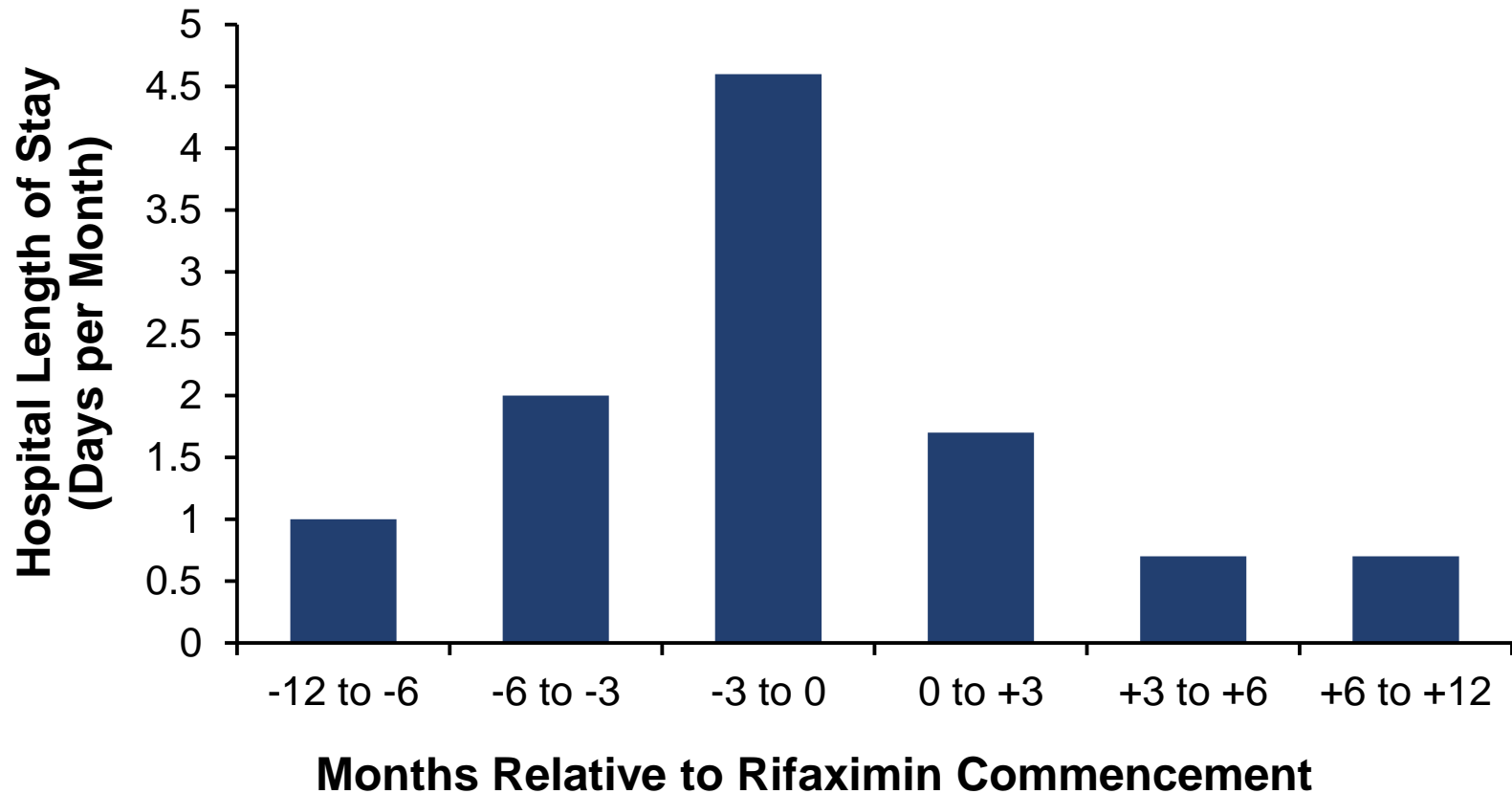
Univariate Analysis of Admission Number and Hospital Length of Stay (HLOS) Before and During Rifaximin

		Before Rifaximin	During Rifaximin	Δ	P
3 months n=227 (69.9%)	Admissions	1.17 (1.15)	0.64 (0.96)	45.3%	<0.001
	HLOS	15.84 (22.46)	7.40 (14.66)	53.3%	<0.001
6 months n=189 (60.0%)	Admissions	1.62 (1.48)	1.02 (1.47)	37.0%	<0.001
	HLOS	20.66 (25.46)	9.66 (16.59)	53.2%	<0.001
12 months n=158 (48.5%)	Admissions	2.11 (1.96)	1.56 (2.39)	26.1%	0.001
	HLOS	24.40 (29.69)	11.53 (18.60)	52.7%	<0.001
All data annualised n=315 (96.6%)	Admissions	3.12 (9.77)	1.98 (4.52)	36.5%	0.042
	HLOS	30.50 (21.03)	21.03 (54.18)	31.0%	0.006

Pattern of Mean Number of Admissions



Mean Length of Emergency Hospital Admissions



The Majority of Overt HE Patients Do Not Receive Proper Management Therapy After Discharge

- **It was determined that >60% of patients did not receive ongoing prophylactic therapy to reduce the risk of HE recurrence after discharge**
- Within an analysis of medical and hospital claims among outpatients who had 1 or more overt HE episodes from 2009 to 2011 during a 3-year period

Rehospitalization Rates Due to Recurrent HE Can Potentially Be Prevented

- In one study, HE was one of the most common causes for possibly preventable rehospitalizations within 1 month after discharge for decompensated cirrhosis[†]
- Some of these rehospitalizations could have been potentially prevented with:
 - Improved Patient Education
 - Telephone Management
 - Other Disease Management Interventions

[†] In a retrospective study of adult patients originally hospitalized with cirrhosis (N=402) and any of the following complications: HE (34%), variceal hemorrhage (20%), spontaneous bacterial peritonitis (13%), renal failure with ascites (24%), or ascites requiring paracentesis (54%) during a 3-year period.^{1,2}

Saab S. *Int J Gen Med.* 2015; Volk et al. *Am J Gastroenterol.* 2012.

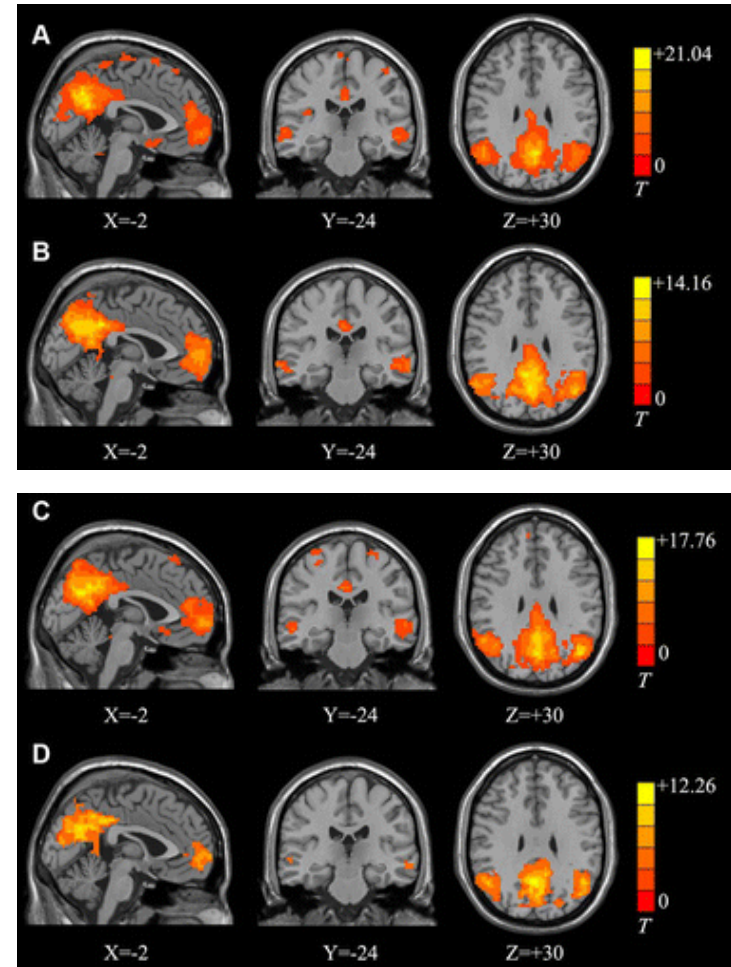
Topics

- Hepatic Encephalopathy
- Economic and Social Burden
- Hospital Readmissions
- **Cognitive Impairment**

Changes in Resting-State Functional MR Imaging

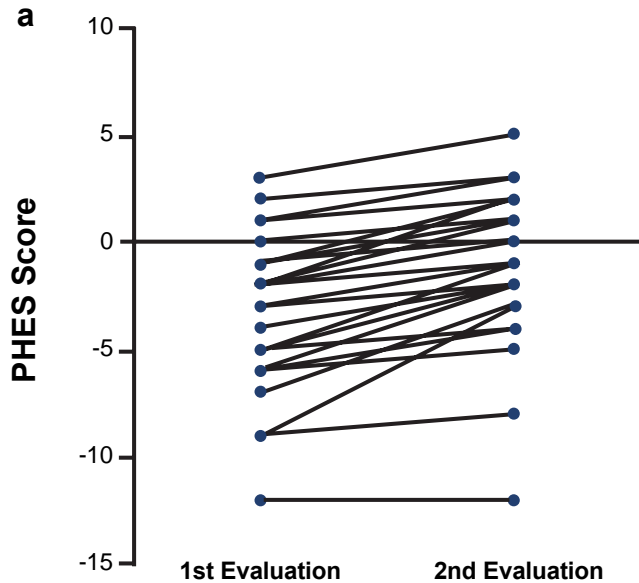
Reduction in Functional Connectivity

- A. Healthy control subjects
- B. The cirrhotic patients without MHE and without previous OHE
- C. The cirrhotic patients with current MHE and without previous OHE
- D. The cirrhotic patients with previous OHE

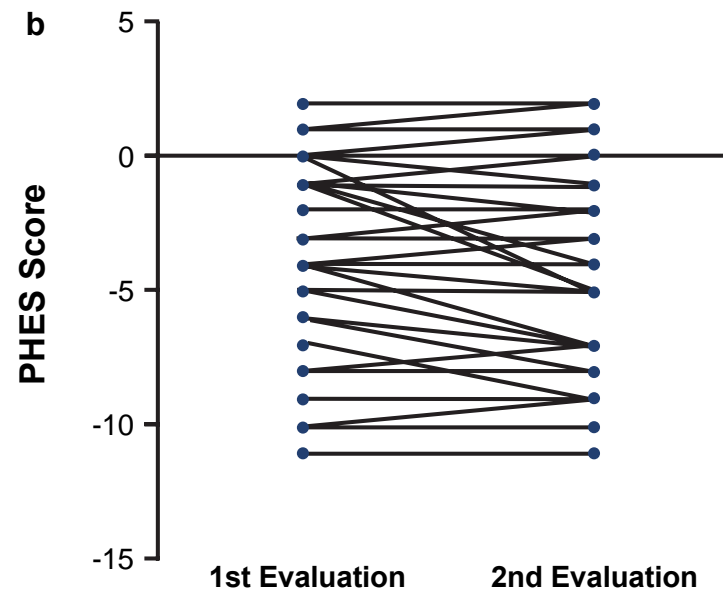


Learning Impairment in Patients with Cirrhosis with a Previous Episode of Overt Hepatic Encephalopathy (HE)

Patients with cirrhosis without prior overt HE episode

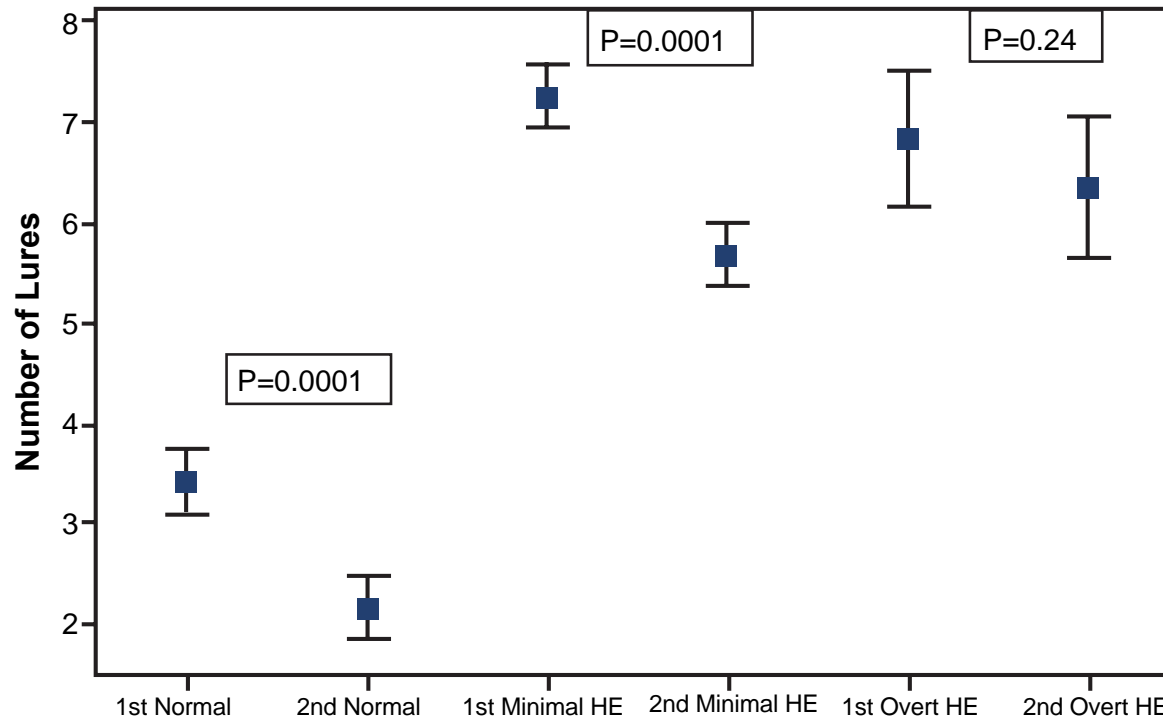


Patients with cirrhosis with a prior overt HE episode

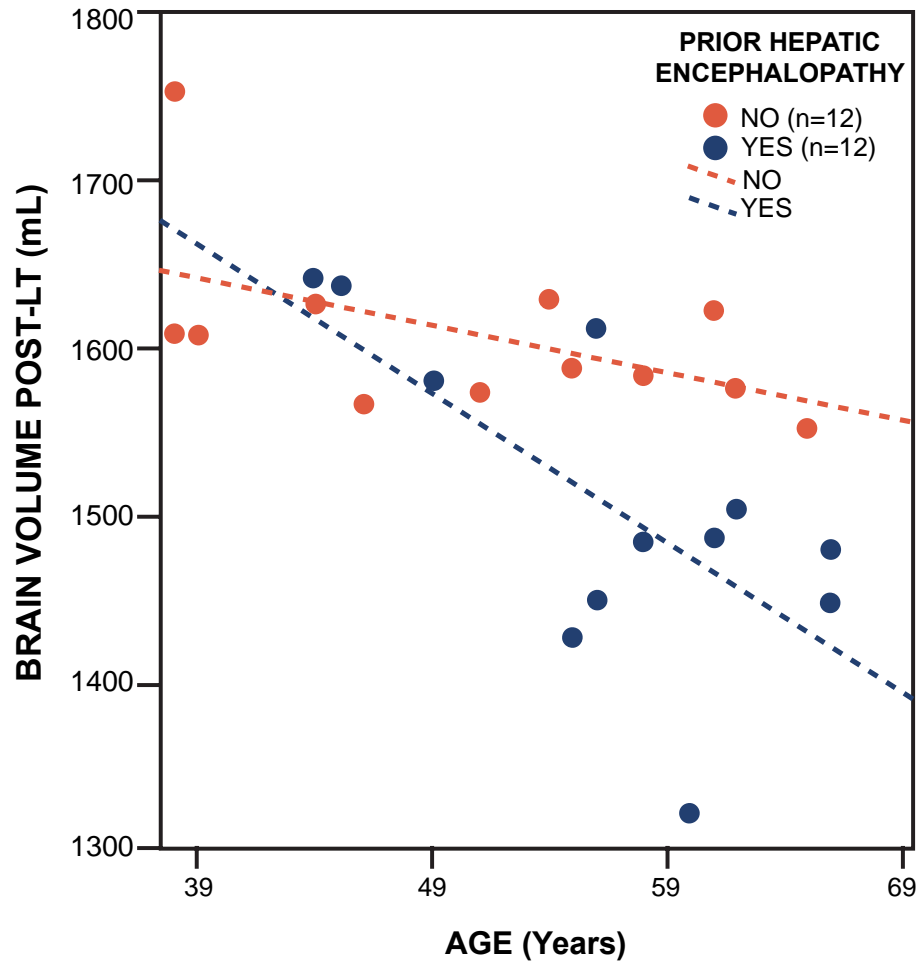


Overt HE Impairs Learning in Patients with Cirrhosis

- Inhibitory control test (ICT)
- Learning impairment in overt HE but not in minimal HE or normals

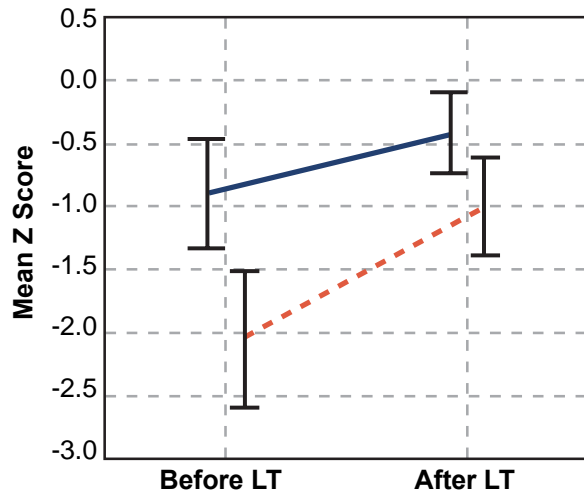


Greater Decline in Brain Volume in Patients with History of HE After Liver Transplantation

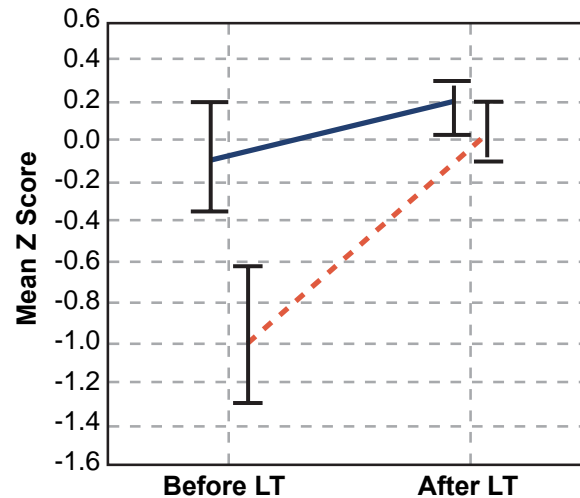


Decreased Cognitive Functions Before and After Liver Transplant According to History of Overt HE

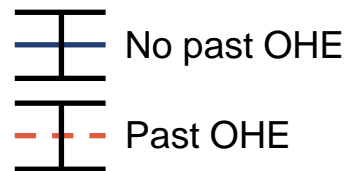
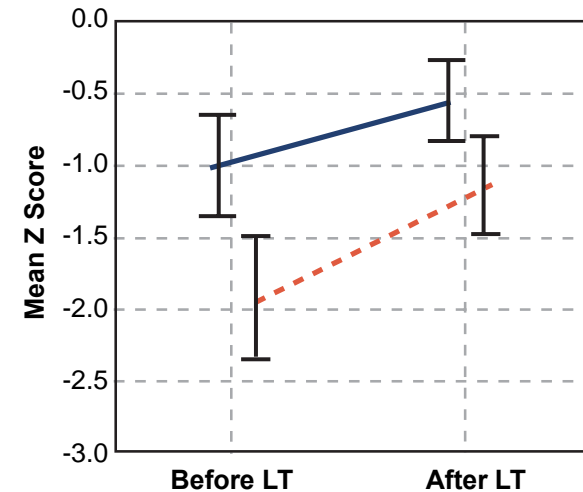
Attention



Memory

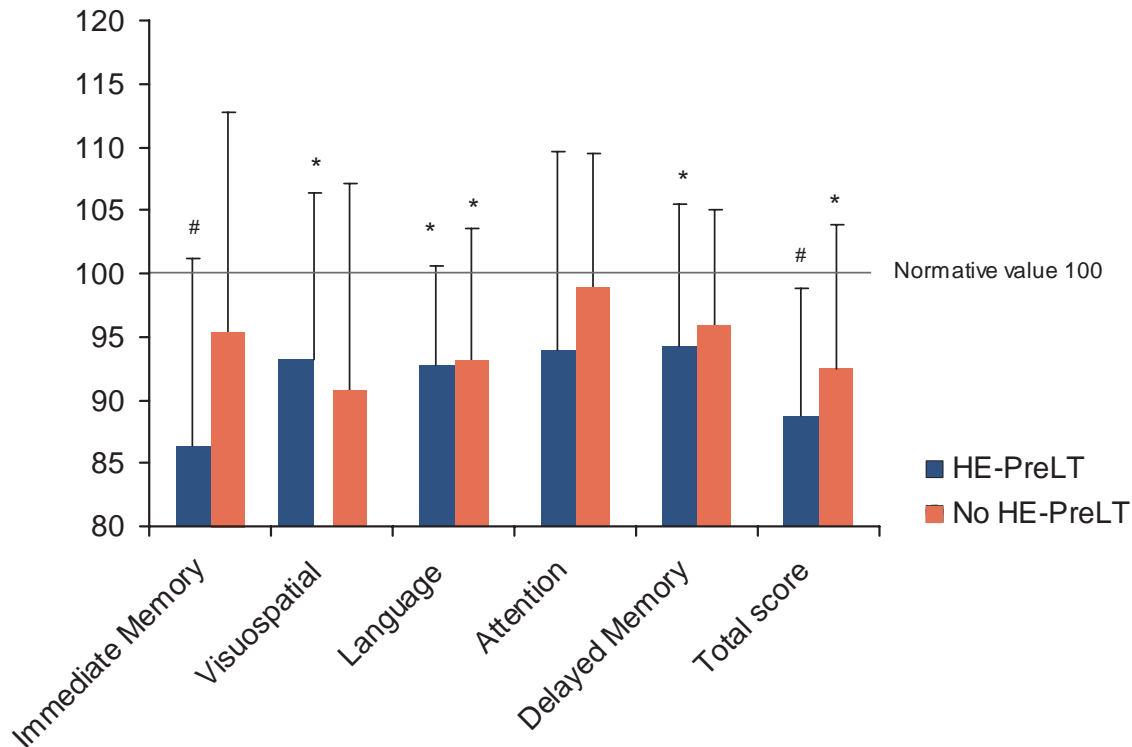


Executive Function



Cognitive Function May Be Compromised, Even Post Liver Transplant

- Study objective: evaluate cognitive function and quality of life in OLT recipients who had suffered from overt HE prior to their procedure
- Patients with cirrhosis with and without overt HE scheduled for liver transplantation (n=39) underwent 2 psychometric batteries* an average of 18 months after liver transplant



*Includes the psychometric hepatic encephalopathy score and Repeatable Battery for the Assessment of Neuropsychological Status. Error bars indicate standard deviation. †Based on results of Repeatable Battery for the Assessment of Neuropsychological Status. ‡ $P < 0.001$ vs normative values. § $P < 0.05$ vs normative values. Sotil et al. *Liver Transpl.* 2009.

Employment in Liver Transplant Recipients, in the United States

Authors (Year)	Number	Follow-up (Months)	Mean Age (Years)	Return to Work
Cowling et al (2004)	152	53	53	36%
Rongey et al (2005)	186	41	55	55%
Sahota et al (2006)	105	34	54	49%
Saab et al (2007)	308	52	51	27%
Huda et al (2012)	21,942	<24	-	45%
Duffy et al (2010)	77	>240	-	35%
Gorevski et al (2011)	91	-	56	38%
Weighted	22,861			45%

Conclusions

- Hepatic encephalopathy is an economic and social burden. Increased burden is realized not only by patients but also experienced by caregivers.
- Hepatic encephalopathy is an important cause of hospital readmission.
- Hepatic encephalopathy is not a completely benign complication of cirrhosis. It may affect future learning that may persist even after liver transplantation.