Update in Portal Hypertension from The 2020 Liver Meeting

Vikrant Rachakonda, MD
Assistant Professor of Medicine
University of Pittsburgh School of Medicine
December 7, 2019

CONFIRM: Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome (LO5)

INTRODUCTION

- **Background**
  - Type HRS 1:
    - SCr ≥ 2.25 mg/dl
    - Doubling of SCr within 2 weeks
    - Lack of improvement (<20% decrease in SCr in 48 hrs after diuretic withdrawal and albumin challenge)
    - Associated with very poor transplant-free survival (20% at 1 month without RRT)
- **Aim:**
  - **To confirm efficacy and safety of terlipressin + albumin versus albumin alone in Type 1 HRS**

METHODS

- Double-blind prospective control trial
- 300 patients randomized 2:1 to terlipressin (1 mg IV every 6 hrs) + albumin (1 gm/kg/d x 2 days then 20 gm/d) versus albumin alone
- Treatment duration: 14 days unless an endpoint occurred, or non-improvement of Cr by day 4
- Outcomes:
  - **Verified HRS Reversal (VHRSR):** 2 consecutive SCr ≤ 1.5 mg/dl, with subjects alive and free of RRT for at least 10 days
  - **HRSR:** SCr ≤ 1.5 mg/dl
  - **RRT**
  - **LT**

RESULTS

Outcome, n (%)	Terlipressin n=199	Placebo n=101	*P* Value
Primary endpoint: VHRSR†	58 (29.1)	16 (15.8)	0.012
HRSR‡	72 (36.2)	17 (16.8)	<0.001
Durability of HRSR (no RRT to Day 30)	63 (31.7)	16 (15.8)	0.003
HRSR in the SIRS subgroup	28 (33.3)	3 (6.3)	<0.001
VHRSR with no recurrence of HRS by Day 30	48 (24.1)	16 (15.8)	0.092
Alive and Transplant-free at Day 90, % (n)	26.1 (52)	26.7 (27)	0.78

RESULTS

- Serious Adverse Event Rates:
  - Terlipressin: 130/200 (65%)
  - Placebo: 60/99 (60.6%)
- Ischemia:
  - Terlipressin: 4.5%
  - Placebo 0%
- No new or unexpected AEs were reported

CONCLUSION

- Terlipressin is effective in improving renal function and achieving HRS reversal in patients with HRS-1 and advanced liver disease.

Cystatin C Predicts Need for Hemodialysis, SLK, and Transplant-Free Survival in Liver Transplant Candidates: 0010

INTRODUCTION

- **Background:**
  - Renal insufficiency is independently associated with reduced survival in end-stage liver disease
  - SCr is a poor surrogate of GFR in patients with cirrhosis and is confounded by:
    - Gender
    - Hepatic synthetic function
    - Muscle mass
    - Race
  - Cystatin C is a 13.3 kDA protein that is completely catabolized in the proximal renal tubule after filtration without return to blood
- **Aim:**
  - To determine the efficacy of Cystatin C in assessing renal function, need for SLK, and mortality risk

METHODS

- Two Center Prospective Cohort Study with 246 patients
- Cys-C obtained at the time of liver transplant evaluation
- Patients were prospectively followed to obtain data on clinical events:
  - LT
  - Need for RRT
  - Need for SLK
  - Transplant-free survival

RESULTS

CHARACTERISTIC	RESULT	NOTES
Liver Transplanted	161 (66%)	Median time 6.6 months (3 d-7y)
Deaths	40 (16%)	
Etiology		
HCV	89 (36%)	
ETOH	52 (21%)	
NAFL	49 (20%)	
Other	56 (23%)	
Male	157 (64%)	
White Race	194 (79%)	
Ascites	174 (71%)	

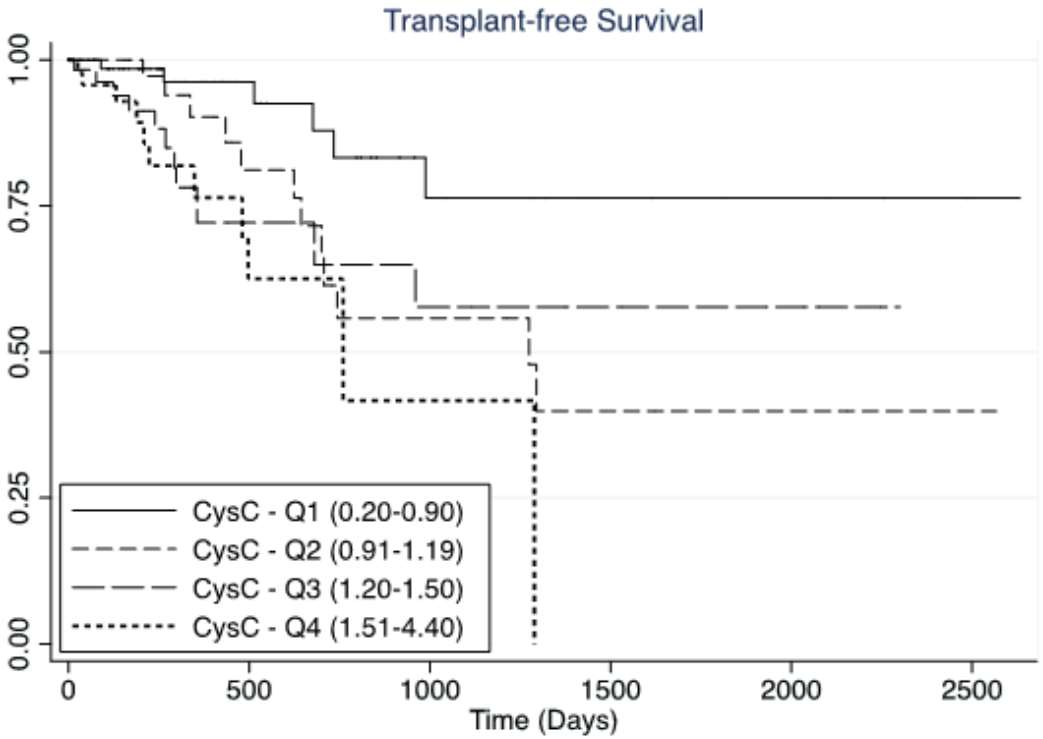
RESULTS

- **ROC for 1-year transplant-free survival:**
  - **MELD-CysC:** AUROC 0.81 (95% CI 0.70-0.92)
  - **MELD:** AUROC 0.78 (95% CI 0.66-0.90)

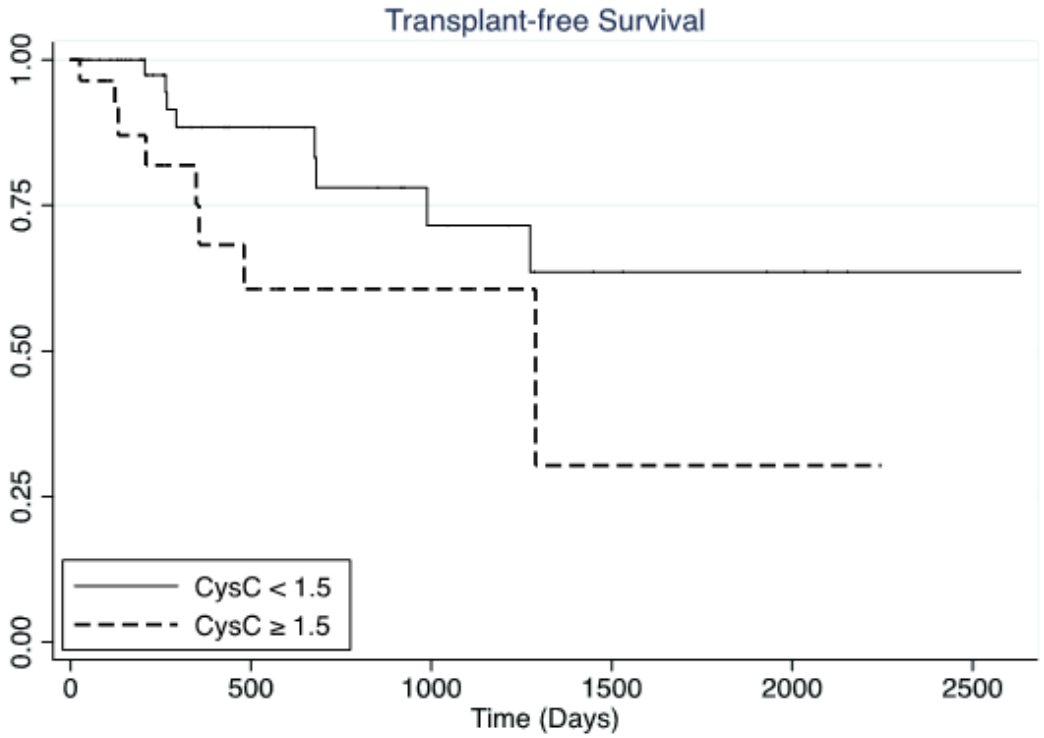
- **CysC ROC for renal-related outcomes:**
  - **Pre-transplant HD:** AUROC 0.77 (0.65-0.90)
  - **SLK:** AUROC 0.89 (0.77-1.00)

RESULTS

Overall, n=246
Quartiles Cystatin C (*p*=0.004)



Women, n=88
Cystatin C <1.5 vs ≥1.5 mg/L (*p*=0.04)



CONCLUSIONS

- Cys C accurately predicts clinical outcomes in LT candidates including pre-LT HD, need for SLK and transplant-free survival

Rifaximin for the prevention of hepatic encephalopathy in patients treated with TIPS: a Multicenter RCT: 0014

INTRODUCTION

- **Background:**
  - Hepatic encephalopathy (PSE) occurs in 30-50% of patients undergoing TIPS placement
  - The role of rifaximin in primary prevention of PSE after TIPS placement is poorly understood
- **Aims:**
  - To determine the efficacy of rifaximin for prevention of a first of PSE after TIPS placement

METHODS

- **Randomized, placebo-controlled trial including 186 patients**
- **Treatment:**
  - Rifaximin 600 mg PO BID
  - Placebo
  - Started 15 days before TIPS and for 6 months after procedure
- **Follow-up period of 1 year**
- **Primary endpoint:** absence of HE at 6 months

RESULTS

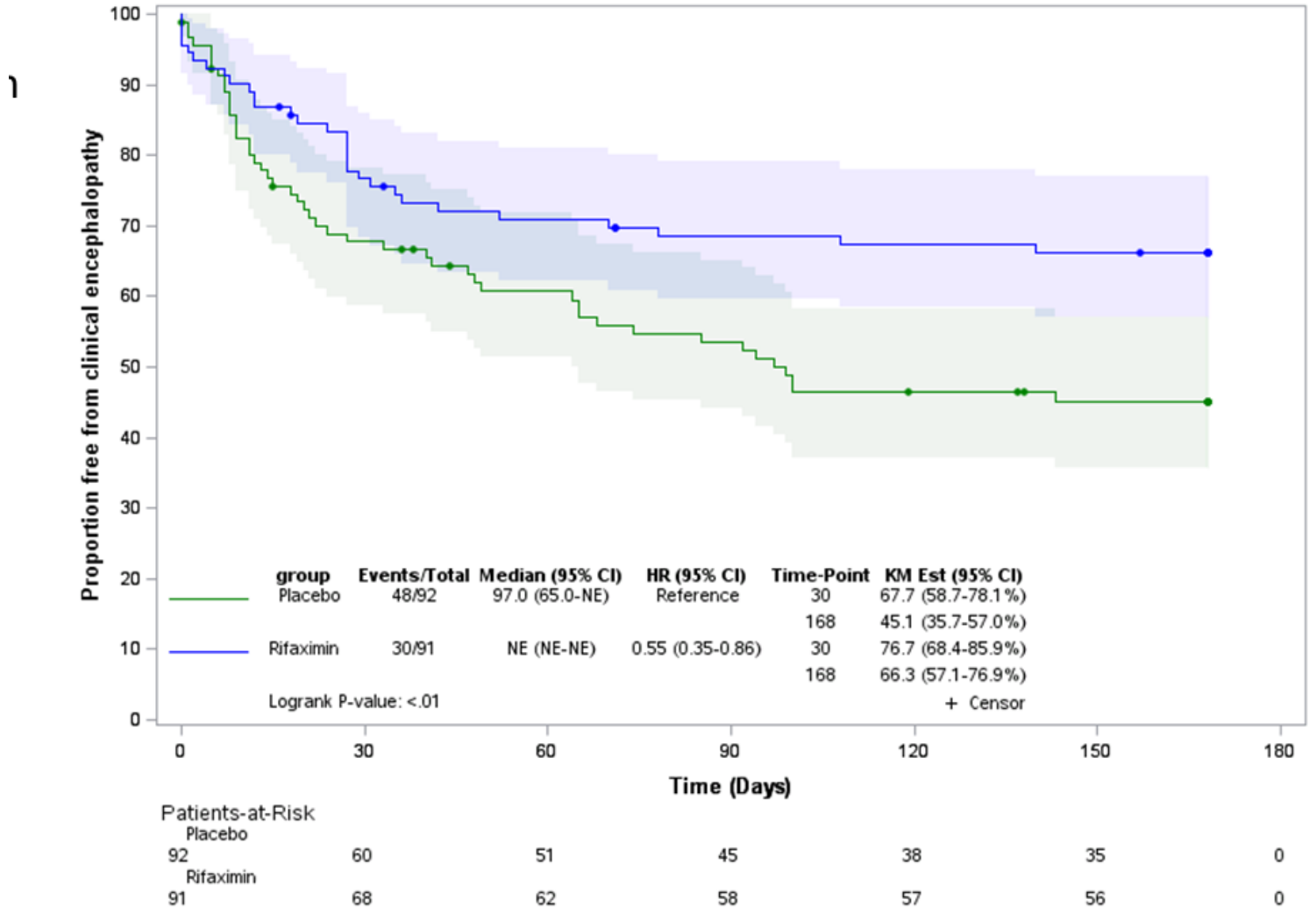
- **Mean Age:** 59.9 ± years
- **Gender:**
  - 144 males
  - 44 females
- **TIPS Indications:**
  - Recurrent Ascites: 86%
  - Prevention of Variceal Rebleeding: 16%
- **Etiology:** 70% ETOH
- **Mean MELD:** 11.9 ± 3.9
- **Mean CTP**: 8.1 ± 1.1
- **20% had pre-TIPS PSE**
- **Follow-up period:** 310 days

RESULTS

6 Month probability of no PSE (p<0.01):
66.3% with RIF
45.1% without RIF

6 Month Transplant-free Survival (p=0.05):
93.2% (88-96%) with RIF
84% (76.7-92.1%)

RIF prevented PSE independently of CTP Class and pre-TIPS PSE



CONCLUSION

- In patients treated with TIPS, preventive rifaximin is associated a lower risk of PSE and higher rate of transplant-free survival at 6 months after TIPS placement

Efficacy of Carvedilol, Endoscopic Variceal Ligation, or a Combination for the Prevention of a First Variceal Bleeding in Child's B and C Cirrhosis with High Risk Varices: 0145

INTRODUCTION

- **Background:**
  - Nonselective beta-blockers (NSBB) are effective for primary prevention of variceal bleeding
  - However, NSBB use is poorly tolerated in patients with Child's Class B and C cirrhosis
  - Bleeding rates after esophageal variceal ligation (EVL) are increased in patients with Child's Class B and C cirrhosis
- **Aim:**
  - **To evaluate the efficacy and safety of NSBB use, EVL, and combination therapy for prevention of first variceal bleed on CTP Class B/C patients with high-risk varices**

METHODS

- **Population:** 270 patients with CTP Class B/C cirrhosis and high risk varices:
  - Large varices (> 5 mm)
  - Small varices with red color signs
- **Randomized 1:1:1 trial (N=90 each) comparing**
  - NSBB: carvedilol
  - EVL
  - NSBB+ EVL
- **Exclusion Criteria:**

HCC	CI to NSBB
PVT	Platelet < 30K
Child's Class A	Prior EVL
CTP > 13	Presence of AKI

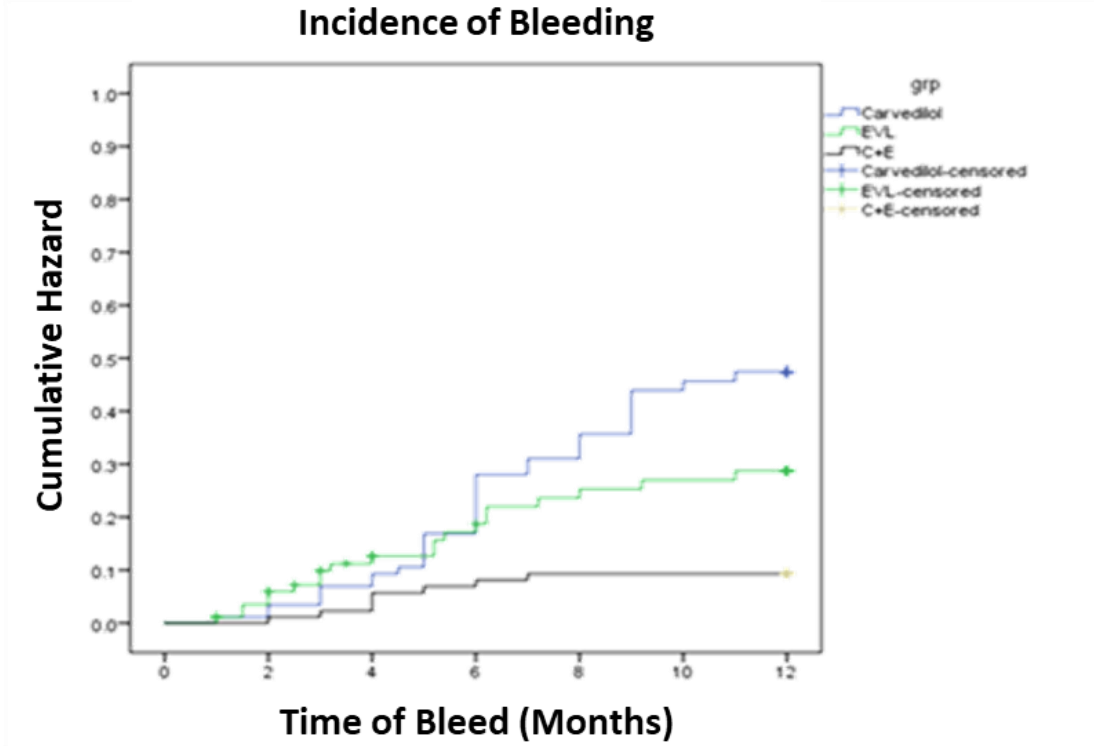
METHODS

- **Primary Outcome:** First Variceal Bleed
- **Secondary Outcomes:**
  - Bleeding-related mortality
  - Improvement in MELD/CTP
  - SBP
  - AKI
  - Shock
  - New Ascites
  - HVPG responses at 3 and 12 months
  - Treatment side-effects

RESULTS

FEATURE	NSBB (Gr 1)	EVL (Gr 2)	EVL+NSBB (Gr 3)	*P*
Age, yr	50.98 (11.5)	50.93 (10.7)	51.7 (10.0)	0.84
Male gender, n (%)	76 (32.6%)	78 (33.5%)	79 (33.9%)	0.50
CTP Score	8.9 (1.1)	9.2 (1.2)	9.1 (1.2)	0.51
Baseline HVPG, mmHg	15.9 (3.3)	16.8 (4.0)	17.4 (3.7)	0.31
Carvedilol dose, mg	15.6 (12.5-18.8)	----------	9.3 (6.3-15.6)	<0.001

RESULTS



Arm		0	2	4	6	8	10	12
Carvedilol	Affected	0	3	6	22	27	33	34
	At risk	90	87	84	68	63	57	56
EVL	Affected	0	5	10	14	18	19	20
	At risk	90	85	80	76	72	71	70
Carvedilol + EVL	Affected	0	1	5	7	8	8	8
	At risk	90	89	85	83	82	82	82

RESULTS

FEATURE	NSBB (Gr 1)	EVL (Gr 2)	EVL+NSBB (Gr 3)	*P* (1 vs 2)	*P* (1 vs 3)
Probability of Bleed	37.8%	22.2%	8.9%	0.04	0.001
Ascites	11.1%	6.6%	8.8%	NS	NS
SBP	3.3%	9.0%	10%	NS	NS
Shock	3.3%	3.3%	1.1%	NS	NS
New AKI	1.1%	2.2%	1.1%	NS	NS
Band Ulcer	--------	6.7%	3.3%	NS	NS
HVPG Response	19 (21.1%)	15 (16.7%)	30 (33.3%)	NS	0.025
(>20% reduction or HVPG < 12)					

RESULTS

- Combination of carvedilol and EVL is more effective than either therapy alone in primary prevention of first variceal bleeding in CTP B and CTP C cirrhosis with high-risk varices.