Welcome!

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Updates from DDW Hepatology

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Objectives

- Review abstracts from DDW highlighting new data from various aspects of hepatology:
  - Hepatocellular carcinoma (HCC)
  - Non-alcoholic fatty liver disease (NAFLD)/endoscopic bariatric therapy
  - Primary biliary cholangitis (PBC)
  - Acute kidney injury in liver disease
  - Alcohol-related liver disease

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Financial Disclosures

- I have no financial disclosures.

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Hepatocellular Carcinoma in Patients With NAFLD: A Meta-Analysis on Prevalence, Risk Factors, Surveillance, Treatment Allocations and Outcomes

- Background:
  - Approximately 25% of the world's population has NAFLD
  - NAFLD-related HCC is the fastest rising cause of HCC in the U.S.
  - Prior studies have shown risk of HCC in non-cirrhotic patients
- Aim:
  - Perform systematic review and meta-analysis to provide pooled estimates for clinical features, surveillance rates, treatment allocation, and survival outcomes of NAFLD-related HCC vs. HCC from other etiologies
- Method:
  - Meta-analysis using Medline and Embase from inception to January 2022

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Tan et al. National University of Singapore.

Hepatocellular Carcinoma in Patients With NAFLD: Results

- 93,851 patient from 60 total studies included, 1980-2021 (19 countries)
- HCC secondary to NAFLD was ~15%
- Higher proportion of NAFLD-related HCC did not have cirrhosis compared to HCC due to other etiologies; 38.5% vs 14.6%
- 29% NAFLD-related HCC patients had surveillance for HCC prior to diagnosis vs. 45.4% HCC secondary to other causes

Figure 2: Proportion of HCC cases without cirrhosis

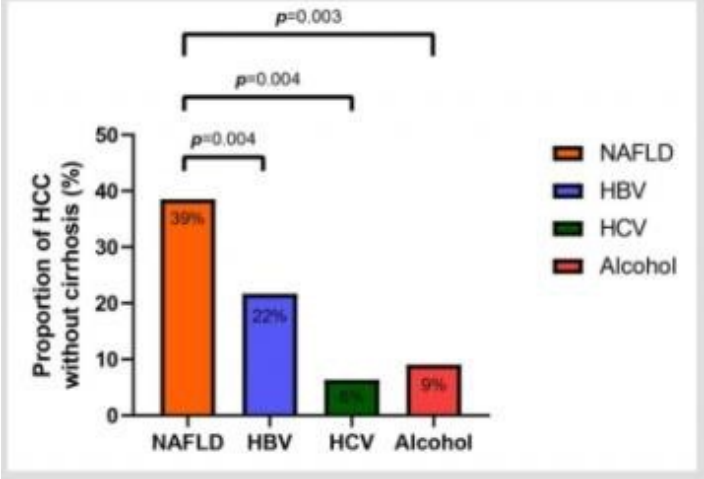
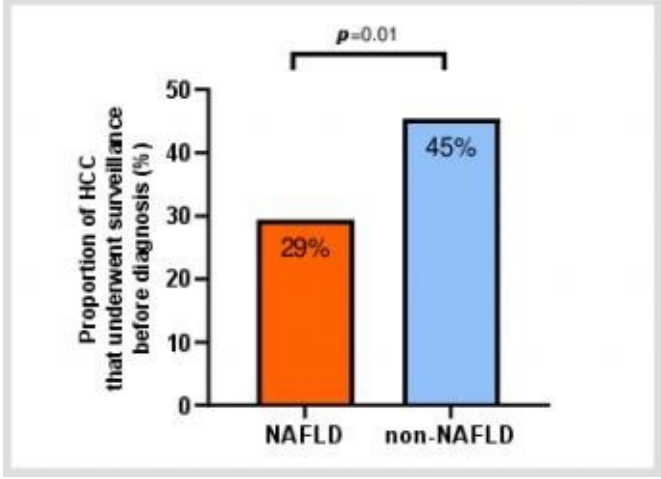


Figure 3: Proportion of HCC cases that underwent surveillance prior to HCC diagnosis



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Hepatocellular Carcinoma in Patients With NAFLD: Results & Conclusion

- Results:
  - NAFLD-related HCC had larger tumor diameter, but no difference in BCLC stage
  - No significant difference in overall survival (OS) between NAFLD-related HCC vs. HCC from other causes
  - Among patients with cirrhosis, NAFLD-related HCC associated with higher mortality (HR 1.79, p=0.004)
- Conclusion:
  - 40% of patients with NAFLD-related HCC did not have cirrhosis and 29% had surveillance prior to HCC
  - NAFLD-related HCC patients presented at similar BCLC stage and had similar survival vs. other HCC
  - Need to improve HCC surveillance strategies for high-risk NAFLD patients without cirrhosis

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Hepatocellular Carcinoma in Patients With NAFLD: A Meta-Analysis on Prevalence, Risk Factors, Surveillance, Treatment Allocations and Outcomes

- Discussion:
  - Claim that ~40% of patients with NAFLD-related HCC did not have cirrhosis is higher compared to previous studies
    - 13%[1] and 20%[2] of patients with NAFLD-related HCC did not have cirrhosis
  - Current NAFLD AASLD guidelines do not recommend HCC surveillance in non-cirrhotics
  - Further studies needed to clarify subgroup of non-cirrhotic NAFLD patients that should undergo HCC surveillance
    - Fibroscan and/or algorithmic approach?

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[1]Mittal et al. *Clin Gastroenterol Hepatol*. 2016; [2]Kanwal et al. *Gastroenterology*. 2018.

Endoscopic Bariatric Therapies Improve Parameters of Hepatic Steatosis Compared to Lifestyle Intervention Alone: Results From Multiple Prospective Studies

- Background:
  - NAFLD is prevalent in ~25% of population worldwide
  - Mainstay of treatment is weight loss, but only ~10% of patient achieve this through lifestyle modifications alone
  - Endoscopic bariatric therapies (EBT) are minimally invasive therapies shown to induce weight loss
- Aim:
  - Determine effect of EBTs on non-invasive markers of hepatic steatosis in patients with obesity
- Methods:
  - Retrospective assessment of prospective trials using EBT for obesity treatment
  - Control patients were treated with lifestyle modifications alone
  - Outcomes assessed between 6 and 12 months follow up

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Rapaka et al. Division of Gastroenterology and Hepatology, Mayo Clinic.

Endoscopic Bariatric Therapies

- Primary Obesity Surgery
  - Endoluminal

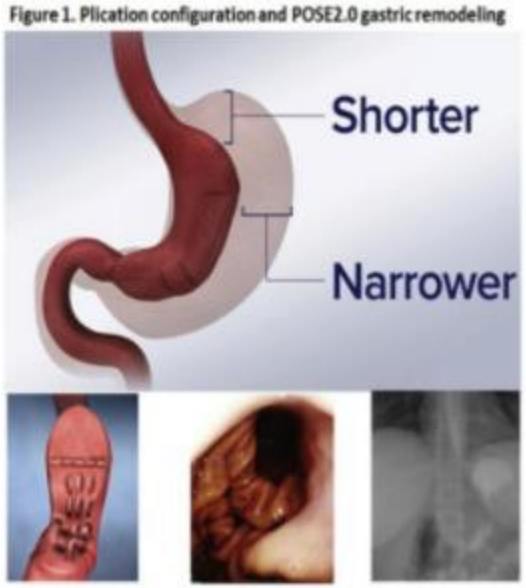


Fig 1. Primary Obesity Surgery Endoluminal (POSE)

- Endoscopic Sleeve

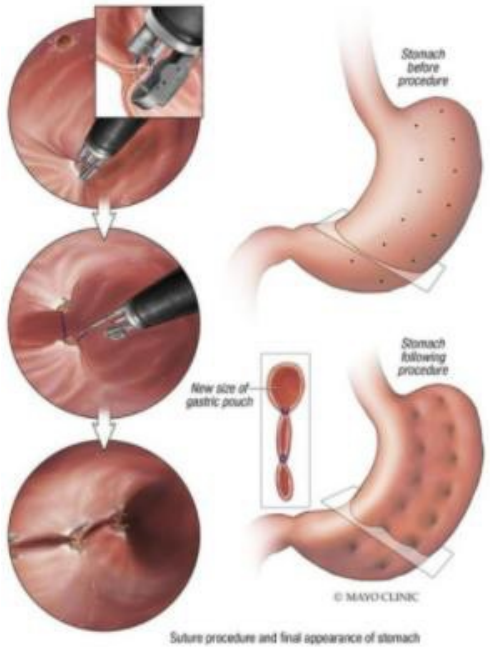
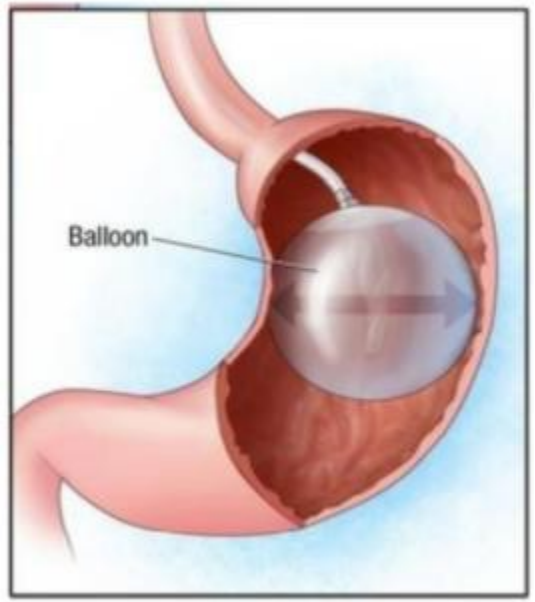


Fig 2. Endoscopic Sleeve Gastroplasty (ESG)

- Intragastric Balloon Gastroplasty



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EBT Patient Population

- 521 EBT patients (389 IGB, 132 gastric remodeling)
- 103 control patients (lifestyle modifications)
- EBT group were older, had higher weight, lower platelets, lower hepatic steatosis index (HIS), and higher FIB-4 scores

Table 1: Baseline Characteristics: EBT vs Controls

	EBT (N=521)	Controls (N=103)	p-value
Age (years)	56.0 ± 11.1	42.0 ± 11.9	**0.0098**
No. of females (%)	82%	73.8%	0.6378
Weight (kg)	104.3 ± 23.1	100.1 ±12.7	**0.0112**
ALT (U/L)	33.9 ± 34.8	34.3 ± 30.7	0.9225
AST (U/L)	27.1 ± 22.5	24.5 ± 18.6	0.2376
ALP (U/L)	78.2 ± 24.8	76.4 ± 25.4	0.5332
Platelets ($x10^3/\mu L$)	269.4 ± 70.3	285.8 ± 61.1	**0.0373**
Albumin (g/dL)	4.3 ± 2.9	4.3 ± 0.4	0.6953
Fasting Blood Sugar (mg/dL)	105.4 ± 35.8	102.3 ± 25.8	0.3339
HbA1c (%)	6.4 ± 1.5	6.1 ± 1.7	0.1984
Insulin (mmol/L)	16.4 ± 9.5	16.9 ± 13.2	0.7317
HOMA-IR (mean)	4.3 ± 3.6	4.8 ± 7.5	0.6219
HSI (mean)	47.6 ± 5.3	52.1 ± 4.5	**0.0002**
FIB-4 (mean)	0.9 ± 1.2	0.7 ± 0.4	**0.0358**
APRI (mean)	0.23 ± 0.32	0.19 ± 0.2	0.2266
NAFLD	-1.9 ± 1.2	-	-

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EBT Results

Primary Endpoints	Secondary Endpoints
Change in:	**Change in:**
1) Hepatic biochemical	1) Hemoglobin A1c (HbA1c)
2) Hepatic steatosis index (HSI)	2) Fasting blood sugar (FBS)
3) AST to platelet (PLT) ratio (APRI)	3) Serum insulin level
4) Fibrosis-4 (FIB-4) score	4) Homeostatic model assessment for insulin resistance (HOMA-IR)

Table 2: Clinical Outcomes: EBT vs Control

	EBT (N=521)	Controls (N=103)	p-value
Δ ALT (U/L)	-11.8 ± 30.0 (278)	-1.0 ± 19.7 (100)	**<0.0001**
Δ AST (U/L)	-5.5 ± 17.4 (17.4)	0.8 ± 12.5 (100)	**0.0001**
Δ ALP (U/L)	-6.3 ± 14.4 (298)	-0.6 ± 13.7 (100)	**0.0006**
Δ Platelets (x10³/µL)	-3.9 ± 42.9 (245)	-0.2 ± 37.2 (100)	0.4524
Δ Albumin (g/dL)	0.0 ± 0.3 (190)	0.0 ± 0.2 (78)	0.6045
Δ Fasting Blood Sugar (mg/dL)	-9.0 ± 33.0 (232)	25.0 ± 176.4 (99)	0.0595
Δ HbA1c (%)	0.0 ± 5.1 (115)	-0.7 ± 1.4 (100)	0.8760
Δ Insulin (mmol/L)	-5.7 ± 12.3 (80)	0.8 ± 19.9 (90)	**0.0110**
Δ HOMA-IR (mean)	-1.8 ± 4.0 (80)	0.3 ± 9.2 (89)	0.0529
Δ HSI (mean)	-5.9 ± 4.6 (205)	-2.4 ± 3.6 (22)	**0.0006**
Δ FIB-4 (mean)	-0.1 ± 1.3 (214)	0.0 ± 0.2 (60)	0.1811
Δ APRI (mean)	-0.1 ± 0.3 (243)	0.0 ± 0.1 (99)	**0.0028**
Δ NAFLD	-1.4 ± 0.7 (165)	-	-

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Endoscopic Bariatric Therapies Improve Parameters of Hepatic Steatosis Compared to Lifestyle Intervention Alone: Results From Multiple Prospective Studies

- Conclusion: EBTs demonstrated greater improvement in hepatic biochemical markers, metabolic markers, and non-invasive measures of hepatic steatosis compared to lifestyle modification alone.
- Discussion:
  - While APRI score significantly decreased in EBT group, initial APRI score was low for both groups-> did fibrosis really change?
  - Limited availability and high cost of EBT are potential barriers to patients

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Higher Doses of Albumin Replacement During Acute Kidney Injury Is Associated With Transplant-Free Survival in Hospitalized Cirrhotic Patients

- Background: Acute kidney injury (AKI) increases the mortality in cirrhotic patient
  - 50% 30-day transplant-free survival for all causes of AKI
  - 10% transplant-free survival for HRS
  - Albumin infusions with vasoconstrictor treatment are 1st-line therapy for HRS
  - Optimal dose and duration of albumin in cirrhotic patients with AKI is unclear
- Hypothesis: Higher doses of albumin within 72 hours of AKI improves transplant-free survival in cirrhotic patients
- Methods: Single-center, retrospective cohort study; 2019-2022
  - Inclusion: Cirrhosis, AKI (Cr > 1.3 and increased 0.3 from baseline)
  - Primary endpoint: transplant-free survival at 60 days
  - 38 total patients

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Scherer et al. Washington University School of Medicine in St. Louis, MO.

Higher Doses of Albumin Replacement During Acute Kidney Injury Is Associated With Transplant-Free Survival in Hospitalized Cirrhotic Patients

Patient Characteristics

N = 38 patients	
Age, years (mean±SD)	57 ± 10
Sex	
Female (%)	23 (60%)
Male (%)	15 (40%)
Ethnicity	
White (%)	33 (87%)
Hispanic (%)	2 (5%)
African American (%)	3 (8%)

Cause of cirrhosis^	
Alcoholic (%)	20 (53%)
Viral hepatitis (%)	6 (16%)
NAFLD (%)	10 (26%)
Other (%)	5 (13%)
MELD ≥ 25 (%)	31 (82%)
Required dialysis (%)	12 (32%)

^Some patients with multiple etiologies

Table 1: Univariate Predictors of Transplant-Free Survival in Patients with Cirrhosis and AKI

	Transplant-free survival	Non transplant-free survival	p-value
Serum albumin on admission (g/dL)	3.01	2.84	.24
Serum albumin on day 3 (g/dL)	4.16	3.64	.013
Days albumin was given	7.42	8.86	.38
Amount of albumin given in the first 24 hours (g)	90.5	61.9	.029
Amount of albumin given in the first 24 hours (g/kg)	1.03	0.73	.032
Amount of albumin given in the first 72 hours (g)	243.2	196.4	.029
Amount of albumin given in the first 72 hours (g/kg)	2.89	2.36	.088
Total amount of albumin given over hospitalization (g)	544.46	538	.37
Total amount of albumin given over hospitalization (g/kg)	6.38	5.97	.41

N=14 N=24 (death or transplant)

- Conclusion: Patients who achieved transplant-free survival received albumin in higher doses within 72 hours (mean 0.96 g/kg/day) than current guidelines recommend in the same time period (1 g/kg up to 100 g on day 1 & 2, and 20 to 40 g per day thereafter).

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Higher Doses of Albumin Replacement During Acute Kidney Injury Is Associated With Transplant-Free Survival in Hospitalized Cirrhotic Patients

- Discussion:
  - Small study, only 38 total patients; need larger, randomized study
  - Baseline creatinine, CKD, and other comorbidities not included in study
  - Etiology of AKI?
  - Co-administration of midodrine, octreotide, norepinephrine etc. for AKI is not included
  - How aggressive is your current administration of albumin? High dose early on? For how long?

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Treatment With Seladelpar in Patients With Primary Biliary Cholangitis (PBC) and Prior Experience With Obeticholic Acid (OCA) or Fibrates

- Background:
  - Up to 40% of PBC patients taking ursodeoxycholicacid (ODCA) do not achieve biochemical treatment response
  - OCA or Fibrates used as adjunct therapy
  - Seladelpar is a potent PPAR-delta agonist; has anti-cholestatic and anti-inflammatory activity in PBC
- Methods: Patients with PBC who had inadequate response or intolerance to UDCA and an ALP ≥ 1.67x ULN were enrolled into open-label Phase 2 study or double-blinded, randomized, placebo-controlled Phase 3 study (ENHANCE)
  - If treated with OCA and/or Fibrates, must have discontinued treatment
  - Data analyzed on patients previously treated with OCA or Fibrates

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Gulamhusein et al. Toronto General Hospital.

Treatment With Seladelpar in Patients With Primary Biliary Cholangitis (PBC) and Prior Experience With Obeticholic Acid (OCA) or Fibrates

Demographics and Baseline Characteristics

Parameters Mean (SD) (Normal range)	Placebo	Seladelpar 5 mg	Seladelpar 10 mg
N	17	26	27
Female/Male	16/1	22/4	24/3
Age, *years*	56 (8)	57 (9)	58 (10)
Age at PBC diagnosis, *years*	47 (7)	49 (9)	48 (9)
Duration of PBC, *years*	9 (6)	7 (5)	10 (7)
BMI, *kg/m²*	31 (6)	29 (8)	28 (5)
Pruritus history, *n (%)*	14 (82%)	21 (81%)	23 (85%)
Cirrhosis, *n (%)*	2 (12%)	4 (15%)	4 (15%)
UDCA dose, *mg/kg/day*	14 (2)	14 (3)	16 (5)
UDCA intolerant, *n (%)*	0	4 (15%)	2 (7%)
ALP (*37-116 U/L*)	334 (149)	345 (140)	307 (128)
ALT (*6-41 U/L*)	48 (27)	55 (26)	48 (23)
Total bilirubin (*0.1-1.1 mg/dL*)	0.7 (0.3)	0.9 (0.4)	0.8 (0.3)
Direct bilirubin (*0-0.2 mg/dL*)	0.2 (0.2)	0.3 (0.2)	0.2 (0.2)
GGT (*7-38 U/L*)	301 (308)	319 (310)	233 (330)
AST (*9-34 U/L*)	38 (18)	47 (19)	42 (17)
Albumin (*3.5-5.5 g/dL*)	4.2 (0.2)	4.0 (0.3)	4.1 (0.3)
Platelets (*140-400 x 10^9/L*)	281 (89)	237 (84)	257 (82)
LDL-C (*50-130 mg/dL*)	152 (29)	133 (49)	131 (50)

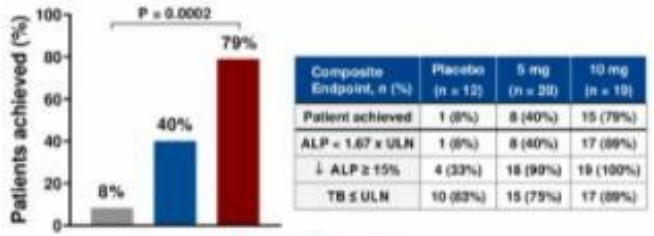
Patients

Patients with Prior OCA/Fibrates Experiences			
n (%)	Phase 2 N = 112	Phase 3 N = 265	Total N = 377
OCA	15	32	47 (12%)
Fibrates	1*	15	16 (4%)
OCA/Fibrates	0	8	8 (2%)
Total	16	55	71 (19%)

* 1 subject who had fibrate was in 2 mg group and was not included for the analysis

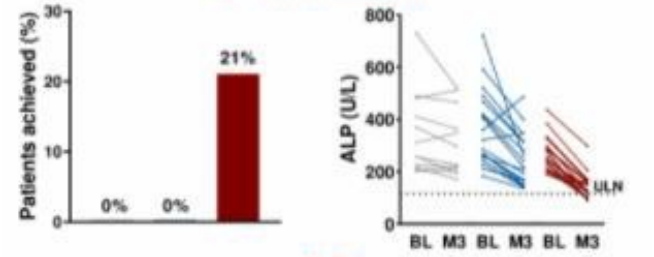
Treatment (n)	Placebo	Seladelpar 5 mg	Seladelpar 10 mg	Total
Baseline	17	26	27	70
Month 3 evaluable	12	20	19	51

Composite Endpoint

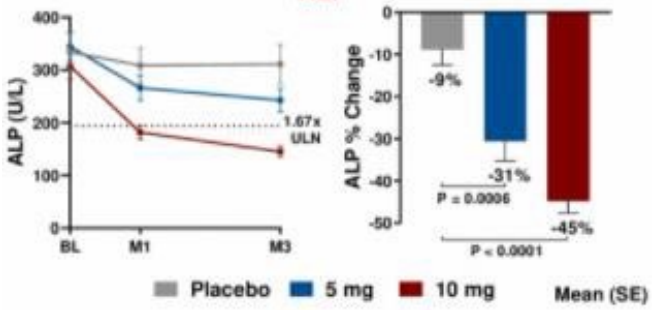


Composite Endpoint, n (%)	Placebo (n = 12)	5 mg (n = 20)	10 mg (n = 19)
Patient achieved	1 (8%)	8 (40%)	15 (79%)
ALP < 1.67 x ULN	1 (8%)	8 (40%)	17 (89%)
↓ ALP ≥ 15%	4 (33%)	18 (90%)	19 (100%)
TB ≤ ULN	10 (83%)	15 (75%)	17 (89%)

ALP Normalization



ALP



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Conclusions & Discussion

- Conclusions: For PBC patients with prior OCA and/or Fibrate use and ALP ≥ 1.67 x ULN, Seladelpar treatment:
  - Appeared safe and well tolerated
  - 79% met composite endpoint in 10 mg group
  - 45% ALP reduction in 10 mg group
  - 21% normalized ALP levels in 10 mg group
  - May offer additional option for patients with difficult to control PBC
- Discussion:
  - Small study, 51 patients evaluated at 3 months
  - Longitudinal follow up needed
  - Global 52-week phase 3 study enrolling patients (RESPONSE)

Safety

Safety Assessment over 1 Year			
Adverse Event (AE) n (%)	Placebo (n = 17)	Seladelpar 5 mg (n = 26)	Seladelpar 10 mg (n = 27)
Patients with at least 1 AE	14 (82%)	24 (92%)	16 (59%)
Any treatment-related AE	5 (29%)	14 (54%)	3 (11%)
Any treatment-related AE ≥ Grade 3 (CTCAE)	0	0	0
Any AE with outcome of death	0	0	0
Any SAE	1 (6%)	3 (12%)	0
Any treatment-related SAE	0	0	0
Any AE leading to discontinuation from Seladelpar	0	2 (8%)	0
Most Common AEs			
Pruritus	3 (18%)	4 (15%)	2 (7%)
Upper respiratory tract infection	1 (6%)	5 (19%)	3 (11%)
Diarrhea	2 (12%)	3 (12%)	3 (11%)
Abdominal pain upper	2 (12%)	3 (12%)	2 (7%)
Nausea	3 (18%)	4 (15%)	0

- SAE: 1 patient on placebo (partial seizures) and 3 patients on 5 mg (1 leukocytosis; 1 cognitive disorder; 1 abdominal pain upper and syncope); all unrelated
- Discontinuation: 2 patients discontinued seladelpar 5 mg due to AE (1 ALT/AST elevation; 1 gastroesophageal reflux disease)

Treatment for Alcohol Dependance Disorder Impacts 30-Day Readmission Rates in Alcoholic Hepatitis

- Background:
  - Prevalence of alcohol use, high-risk drinking, and alcohol use disorder (AUD) are increasing in the US
  - Alcoholic hepatitis (AH) associated with high morbidity and mortality
  - Recurrent hospitalization is common in AH and alcohol abstinence is the only prevention
- Aim: To evaluate the impact of counseling and treatment for alcohol abuse and dependence on readmissions from AH
- Methods: Retrospective analysis using Nationwide readmissions database in 2018
  - Age ≥18 and diagnosis of AH or alcohol use with secondary diagnosis of AH
  - Patients who received inpatient counseling, psychotherapy/cognitive behavioral therapy, pharmacotherapy were identified using ICD-10 procedure codes
  - Impact of counseling on 30-day readmission was evaluated

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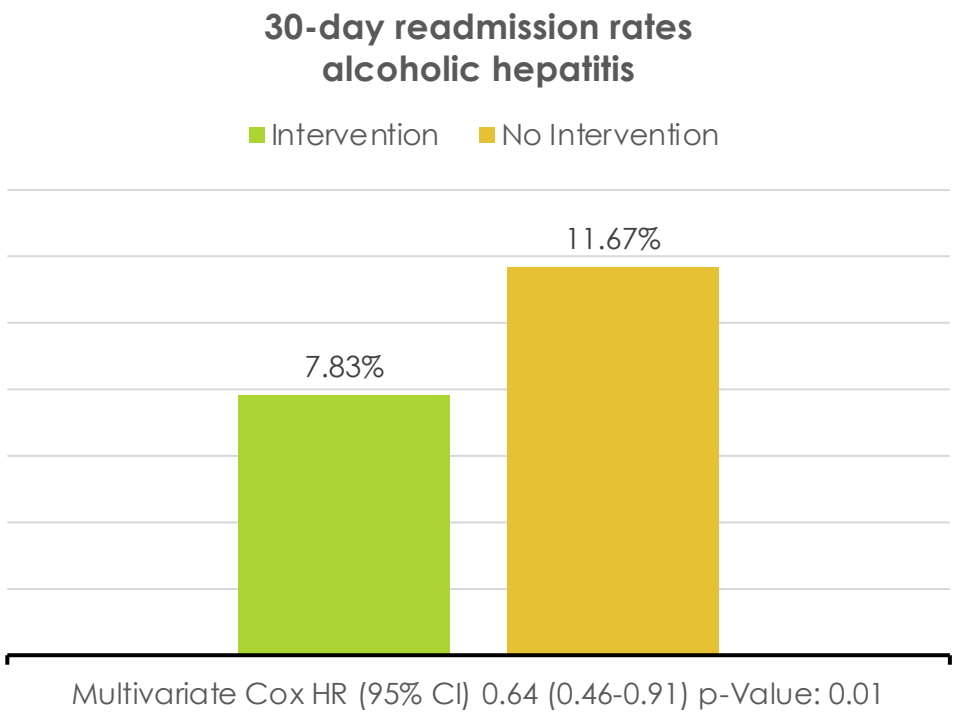
Gangu et al. University of Missouri.

Treatment for Alcohol Dependance Disorder Impacts 30-Day Readmission Rates in Alcoholic Hepatitis

Table 1: PATIENT LEVEL CHARACTERSTICS			
VARIABLES	**ALCOHOLIC HEPATITIS WITH COUNSELING**	**ALCOHOLIC HEPATITIS WITHOUT COUNSELING**	**p- Value**
SAMPLE SIZE (N)	1,552	44,065	
READMISISON RATE (%)	7.83%	11.67%	0.008
MEAN AGE (SD) YEARS			0.32
Female	45.07(12.27)	45.99(12.22)	
Male	45.88(12.16)	46.39(12.26)	
AGE GROUPS			0.42
18-44	46.89%	45.1%	
45-64	48.38%	48.86%	
≥65	4.72%	6.04%	
SEX (FEMALE)	29.82%	32.47%	0.24
MEDIAN INCOME IN PATIENTS ZIP CODE ($)			0.78
<$45,999	25.89%	25.11%	
46,000 – 58,999	26.91%	27.3%	
59,000 - 78,999	24.09%	26.61%	
≥79,000	23.1%	20.98%	
INSURANCE STATUS			0.61
Medicare	13.72%	14.4%	
Medicaid	43.49%	40.07%	
Private	30.31%	30.45%	
Self pay	12.47%	15.09%	
HOSPITAL LOCATION			0.006
Large metropolitan area	71.54%	54.75%	
Small metropolitan area	22.97%	38.12%	
Micropolitan area	4.95%	5.57%	
Not metropolitan or micropolitan area	0.55%	1.56%	
HOSPITAL BEDSIZE			0.87
Small	20.19%	19.24%	
Medium	32.02%	29.67%	
Large	47.8%	51.09%	
HOSPITAL TEACHING STATUS	66.36%	72.12%	0.50
HOSPITAL OWNERSHIP			0.03
Government/Public	7.23%	10.61%	
Private (Not for profit)	67.9%	79.07%	
Private (Investor-owned)	24.87%	10.31%	
DISPOSITION			<0.001
Regular	86.7%	77.42%	
Skilled Nursing Facility	3.19%	9.2%	
Home health	2.64%	5.75%	
Left against medical advice	7.47%	7.62%	



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Treatment for Alcohol Dependance Disorder Impacts 30-Day Readmission Rates in Alcoholic Hepatitis

- Conclusions:
  - Therapy for alcohol abuse can help prevent readmissions from alcoholic hepatitis and it is an under-utilized tool for management
  - Therapy should ideally be implemented for all patients hospitalized with AH and all disorders related to alcohol dependence to impact disease burden and readmission
- Discussion:
  - Large study, but retrospective
  - Readmission rates for pharmacotherapy, counseling, and CBT not compared
  - Only a very small percentage of patients received treatment for AH
  - Lack of access to psychiatric care remains a barrier to treatment

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Thank You!!

QUESTIONS?