AASLD Nov. 4-8, 2022

The Liver Meeting®

WASHINGTON D.C.

The Best of The Liver Meeting®

PORTAL HYPERTENSION/CIRRHOSIS

About the program:

Best of The Liver Meeting 2022 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

Use of these slides:

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Assessment of kidney function in patients with decompensated cirrhosis: Does removing race variable improve performance of new GFR equations?

Objective

To evaluate the performance of novel estimated GFR (eGFR) equations as compared to protocol measured GFR (mGFR) in patients listed for liver transplantation.

Methods

Comparison of eGFR equations particularly CKD-EPI AS (age, sex, no race, Inker NEJM 2021) and GFR Assessment In Liver disease (GRAIL, Asrani SK Hep 2019) to mGFR measurements by iothalamate clearance at protocol time points before LT in 2090 patients listed for liver transplantation between 1985 and 2015.

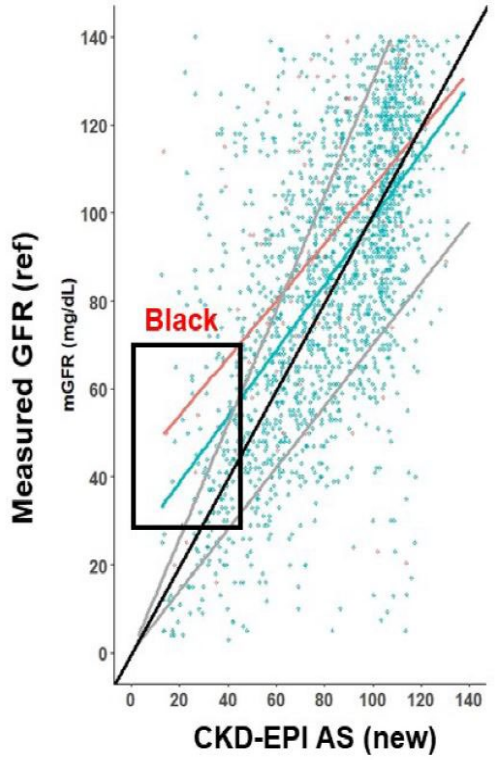
Bias was defined as difference between mGFR and eGFR.

Main Findings

- For mGFR <30ml/min, CKD-EPI AS overestimated GFR by 18 ml/min with low precision. This was worse than other GFR equations (Table).
- For mGFR <30ml/min, GRAIL had the lowest bias, difference between mGFR and eGFR, followed by MDRD-6.
- Among Black patients, variation in GFR estimation was higher than non-Black patients by CKD-EPI AS (17.9 ml/min vs 6 ml/min) (Table and Figure).

	Overall*	GFR<30*	Ascites*	Black*	Non-Black*
Bias (Difference vs mGFR (ml/min/1.73m^2))					
CKD-EPI AS (new)	**6.67**	**-18.50**	**3.84**	**17.87**	**5.96**
CKD-EPI 2012	8.99	-16.49	6.54	7.56	9.17
MDRD 4	11.75	-15.32	9.65	10.58	11.78
MDRD 6	16.25	-10.32	15.35	14.46	16.32
GRAIL	**4.06**	**-7.35**	**2.87**	**3.78**	**4.75**
Percent Agreement within 30% of Measured GFR (P30)					
CKD-EPI AS (new)	**67.85**	**13.39**	**64.07**	**66.15**	**68.05**
CKD-EPI 2012	67.94	16.07	64.72	68.46	67.85
MDRD 4	62.97	21.43	60.34	66.92	62.66
MDRD 6	61.42	32.14	58.43	63.08	61.34
GRAIL	**63.09**	**62.04**	**57.20**	**64.84**	**63.05**
Percent Agreement between eGFR and Measured GFR Categories					
CKD-EPI AS (new)	**55.74**	**18.75**	**51.61**	**53.08**	**55.93**
CKD-EPI 2012	54.55	21.43	50.32	64.61	53.98
MDRD 4	49.12	25.89	47.24	63.08	48.22
MDRD 6	45.54	33.93	42.16	51.54	45.03
GRAIL	**56.09**	**49.11**	**49.75**	**66.15**	**55.52**

*Difference between mGFR and eGFR, negative implying overestimation and positive implying underestimation



Conclusions

Implementation of novel eGFR equations (CKD-EPI AS) without race may not accurately capture true kidney function in cirrhosis especially in low GFR and Black patients.

Fallahzadeh MA, et al., Abstract 4.

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Three vs. two doses of COVID-19 mRNA vaccine and SARS-CoV-2 infection among patients with cirrhosis

Objective

Cirrhosis is associated with immune dysregulation and hyporesponsiveness to several vaccines including COVID-19. We aimed to study the association of receipt of three vs. two doses of a COVID-19 mRNA vaccine in patients with cirrhosis.

Methods

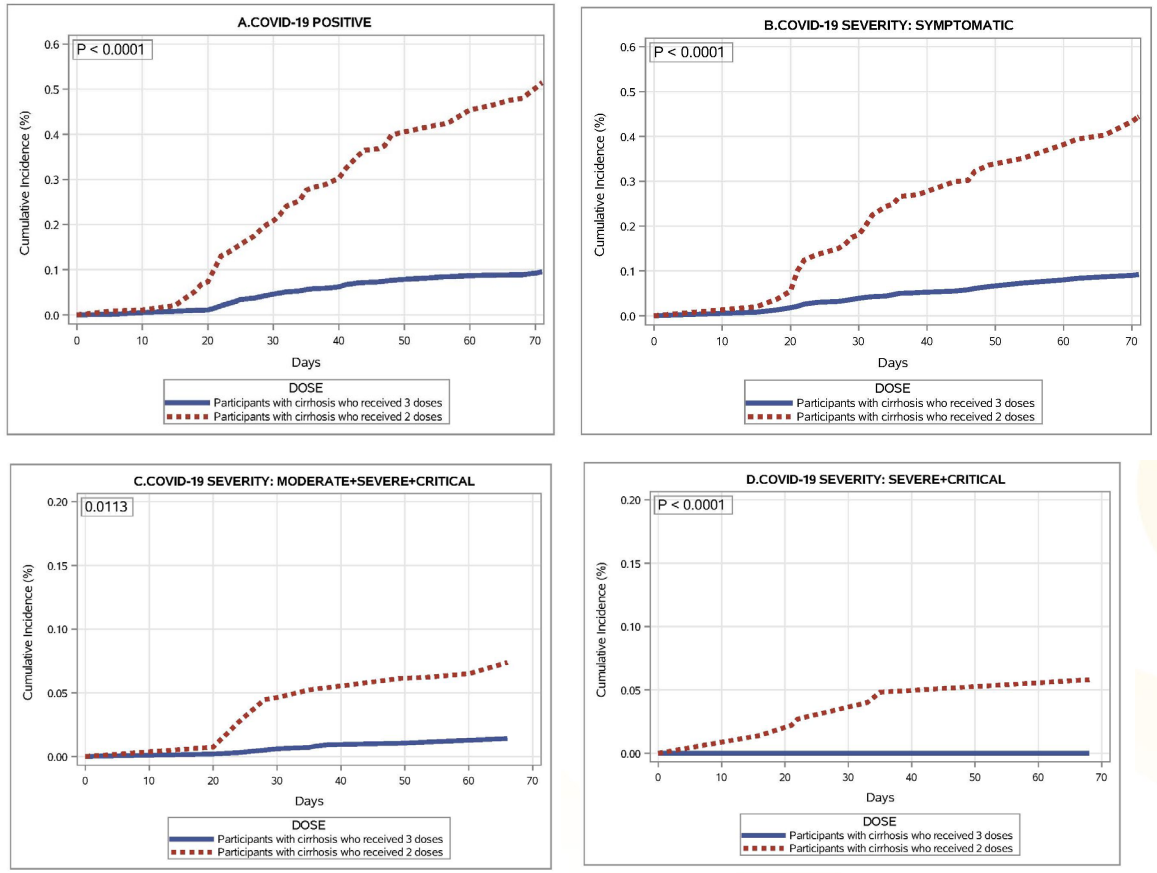
Retrospective study of patients with cirrhosis from the VOCAL cohort.

Main Findings

- Participants who received three doses (n=13,041) were propensity matched with 13,041 controls who received two doses.
- Receipt of the third dose of a COVID-19 mRNA vaccine was associated with an 80.7% reduction COVID-19 (95% CI 39.2-89.1), 80.4% reduction in symptomatic COVID-19, 80% reduction in moderate/severe or critical COVID-19 (95% CI 34.5-87.6%), 100% reduction in severe or critical COVID-19 (95% CI 99.2-100.0), and a 100% reduction in COVID-19–related death (95% CI 99.8-100.0).

Conclusions

Administration of a third dose of a COVID-19 mRNA vaccine is associated with a more significant reduction in COVID-19 in cirrhosis than in the general population suggesting that the third dose may overcome vaccine hyporesponsiveness in cirrhosis.



Binu J, et al., Abstract 8.

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Early versus standard initiation of terlipressin for HRS-AKI in ACLF – A randomized controlled trial (*eTERLI study*)

Objective:

To investigate whether early initiation of terlipressin (eTerli) therapy can improve response in HRS-AKI patients.

Methods:

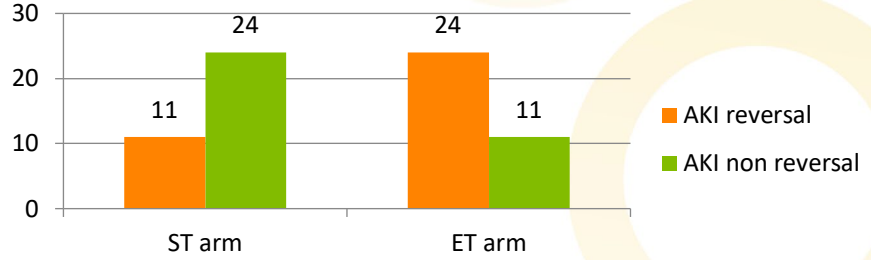
- A prospective, randomized, single center open label study
- Consecutive ACLF patients with stage II/III AKI despite albumin resuscitation (40 g) for 12 hours were randomized to receive early terlipressin at 2 mg/24 hour plus albumin (**ET**, n=35) or standard therapy (**ST**, n=35) with albumin alone for 48 hours followed by terlipressin.
- The primary end-point was AKI reversal by day 7. Secondary end-points included need for dialysis, treatment-related adverse effects and mortality at day 28 and Day 90.

Main Findings:

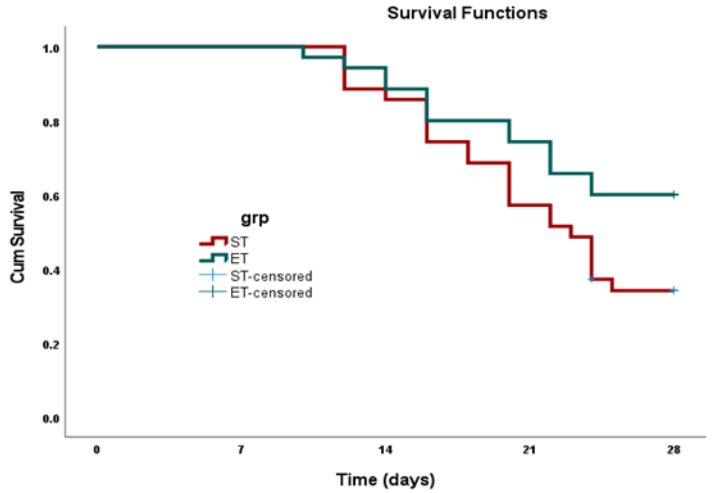
- Baseline parameters including AKI stage and ACLF AARC scores in two groups were comparable.
- Full AKI response at day 7 was observed in 24/35 (68.6%) patients in ET group compared to 11/35(31.4%) in ST group [*P*-0.03]. Full AKI response at day 3 was observed in 11/35 (31.4%) patients in ET group vs. 4/35(11.4%) in ST group [*P*-0.04]. Patients in ET group showed significant improvement in MAP (68.2 ± 1.2 to 82.3 ± 1.4 mm Hg; *P*-0.05) and urine output (26.4 ± 0.9 to 52.4 ± 1.2 ml/h; *P*-0.001) at day 3. Five patients in each group developed progressive AKI requiring dialysis. The total dose of albumin (baseline to day 7) was higher in ST (177.5 ± 40.3g) than ET group (149.1 ± 41.8g) [*P*-0.006].
- Significantly more patients died within 28 days in ST than ET group [23/35; 65.7 % vs. 14/35: 40%, *P*-0.031]. The 90-day mortality in ST group was higher (69.6% vs. 57.2%; *P*-0.14). Baseline MELD score [HR: 0.987 (95%CI: 0.864-3.211); P-0.02], HE at presentation [HR: 4.405(95% CI: 1.776-10.927); P-0.001] and admission blood urea [HR: 1.007(95%CI: 1.000-1.013); P-0.036] were independent predictors of 28-day mortality. Overall, 9 patients had terlipressin related adverse effects, none was life threatening.

Conclusions:

In patients with ACLF, early initiation of terlipressin for AKI persisting despite 12 hours of volume expansion with albumin helps in early reversal of AKI, improvement in hemodynamic parameters and regression of ACLF stage with significant short-term mortality benefit.



AKI reversal by Day 7 (P value- 0.030)



ET group showed better 28-day survival as compared to ST group (p value 0.031)

Singh H, et al., Abstract 12.

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Statin use is associated with a reduction in acute on chronic liver failure-related short-term mortality

Objective

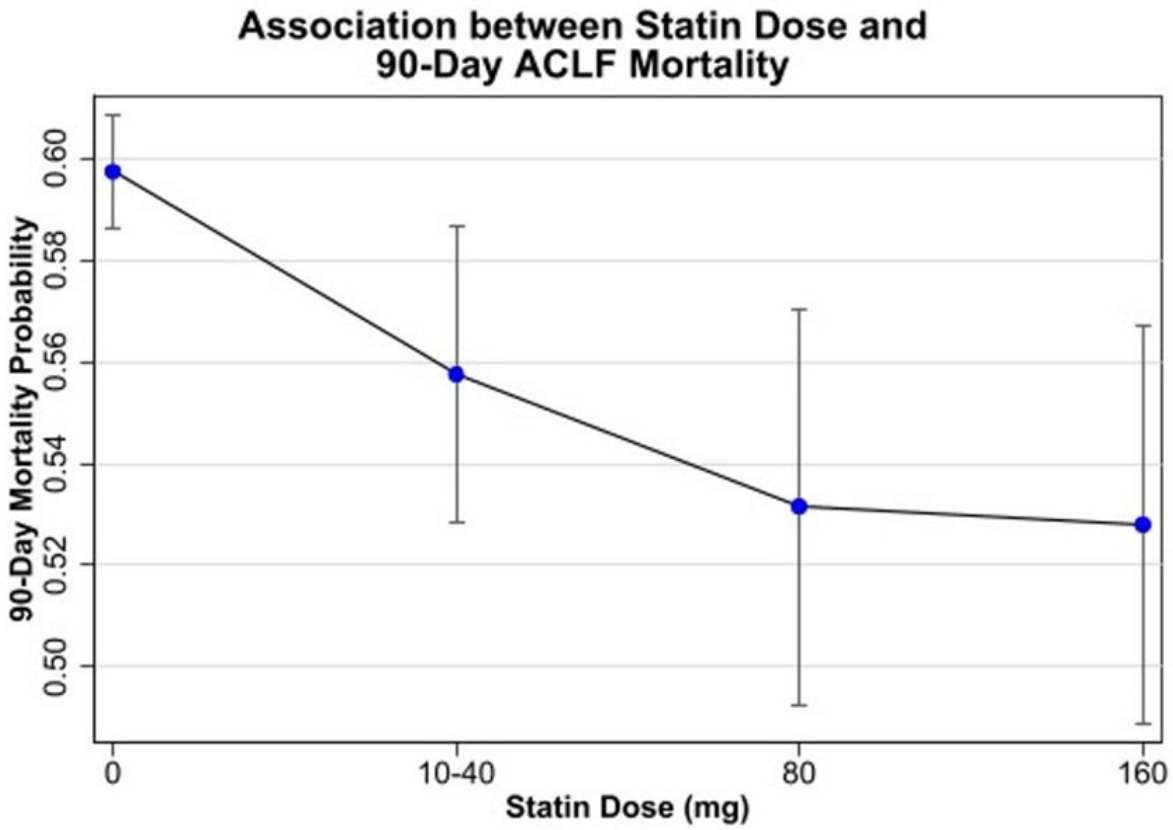
To determine the association between statin exposure and short-term mortality among patients hospitalized with high-grade Acute on Chronic Liver Failure (ACLF)

Methods

- Design: retrospective cohort study of Veterans Health Administration patients with cirrhosis who were hospitalized with a high grade (2 or 3) ACLF event per EASL criteria
- Exposure: continuous statin exposure for at least 90 days prior to hospitalization with high-grade ACLF
- Outcome: 28- and 90-day ACLF-related mortality
- Analysis: multivariable logistic regression modeling

Conclusions

- Statin exposure was associated with reduced odds of 28-day and 90-day mortality in patients with cirrhosis hospitalized with high-grade ACLF (OR 0.83 28-day, OR 0.78 90-day)
- Increasing statin dose exposure was associated with further reduction in 90-day ACLF-related mortality



Chapin S, et al., Abstract 119.

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PNPLA3-rs738409-GG genotype is associated with high incidence of cirrhosis among patients with non-alcoholic fatty liver disease, even in the absence of significant baseline fibrosis

Aim

Evaluate impact of *PNPLA3*-rs738409 genotype on cumulative incidence of cirrhosis in NAFLD

Methods

Retrospective cohort study of the Michigan Genomics initiative, with NAFLD defined by ALT elevations in the absence of chronic liver disease

Main Findings

Patients with *PNPLA3*-rs738409-GG genotype have greatly increased cumulative incidence of cirrhosis, across several subgroups, even excluding those with FIB4 ≥ 2.67 (Table)

Conclusions

- Patients with *PNPLA3*-rs738409-GG genotype are at much higher risk of cirrhosis
- Routine *PNPLA3* genotyping may improve risk stratification in NAFLD

Cohort	*PNPLA3*-rs738409 genotype		
	CC (lowest risk) or CG	GG (highest risk)	P value
All	3.15 (2.59-3.80)	8.89 (5.75-13.12)	<0.0001
Diabetes	5.09 (3.70-6.83)	16.43 (8.20-29.40)	<0.0001
No diabetes	2.51 (1.95-3.20)	6.53 (3.57-10.96)	0.00084
Obesity	3.70 (2.80-4.80)	9.21 (4.76-16.09)	0.0022
No obesity	2.32 (1.54-3.36)	6.80 (2.50-14.81)	0.012
ALT >= 2x ULN	4.16 (3.00-5.62)	13.85 (8.07-22.17)	<0.0001
ALT < 2x ULN	2.74 (2.13-3.48)	5.05 (2.18-9.95)	0.10

Chen V, et al, Abstract 179.

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GB1211, an oral galectin-3 inhibitor, in decompensated cirrhotic patients: Initial findings from the Phase 2 randomized, placebo-controlled GULLIVER-2 trial

Objective

To investigate the safety, PK, and exploratory efficacy of GB1211, an oral, potent, high-affinity Gal-3 inhibitor, in patients with decompensated cirrhosis (Child-Pugh B), irrespective of etiology.

Methods

Double-blind 12-week trial comparing GB1211 to placebo in 30 patients randomized 1:1. Exploratory endpoints: clinical laboratory tests, elastography (VCTE), and biomarkers.

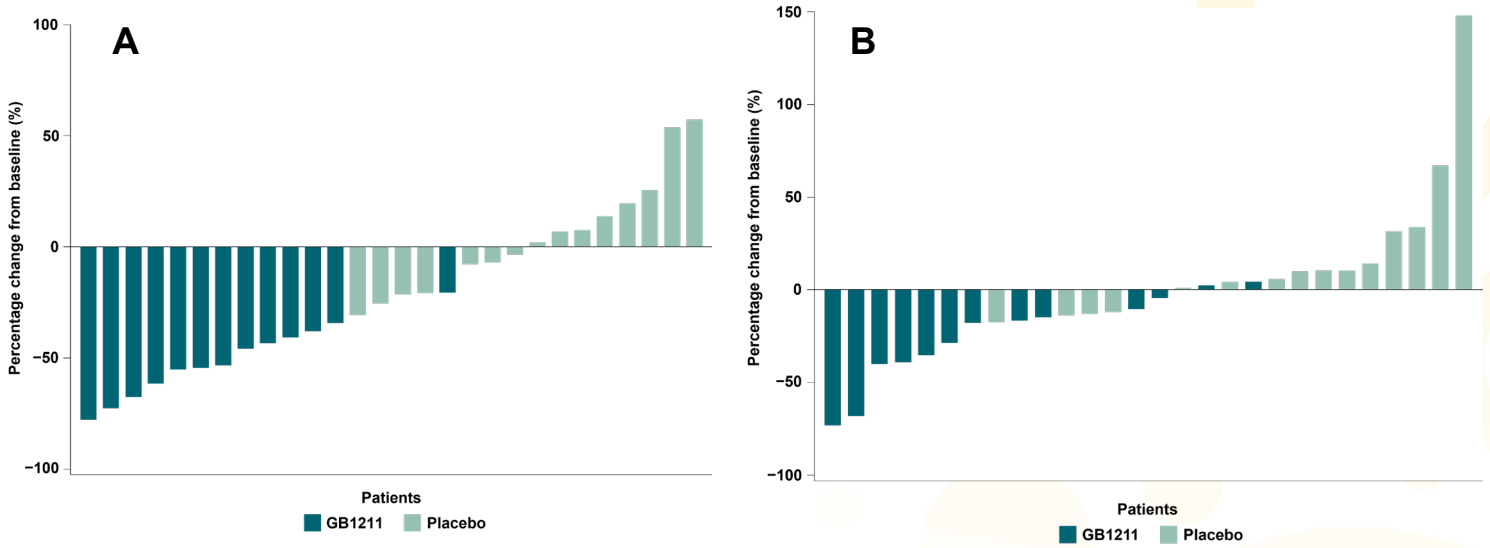
Main Findings

- GB1211 was well-tolerated and demonstrated target engagement with a reduction in serum Gal-3 levels.
- GB1211 exhibited predictable PK with steady-state reached by Week 1.
- GB1211 showed progressive reductions in ALT, AST, and GGT, which were preserved two weeks after the end of treatment.
- VCTE demonstrated a decrease in liver stiffness and CAP values.

Conclusions

- Gal-3 reduction by GB1211 showed fast onset and continuous improvements in liver enzymes, as measured by ALT, AST, and GGT, over 12 weeks, and was well-tolerated.
- To our knowledge, this is the first clinical study showing encouraging effects on liver parameters over a short period of time in patients with decompensated cirrhosis of non-viral etiology.
- Results warrant further study of GB1211 in patients with severe liver disease.

Figure. GB1211 showed improvements in ALT (A) and AST (B), compared with placebo, at Week 12*



*Two patients in the GB1211 group did not have Week 12 data due to withdrawal.

ALT, alanine transferase; AST, aspartate transferase; CAP, controlled attenuation parameter; Gal-3, galectin-3; GGT, gamma-glutamyl transferase; PK, pharmacokinetics; VCTE, vibration-controlled transient elastography

Lindmark B, et al., Abstract LO14.

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