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FCR NIT Literature Review

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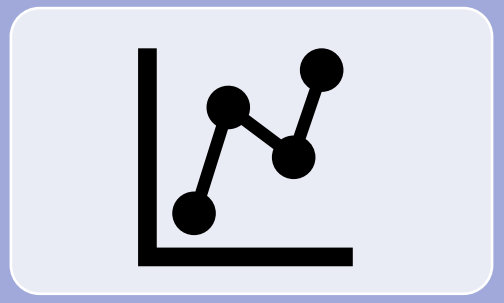
Berkeley Public Health

OUTLINE

Literature Review Methods



NIT data: i) Prognosis-predicting Liver Related Events (LRE) and ii) response to treatment

- LSM
  - VCTE
  - MRE
- Plasma markers of fibrosis
  - ELF
- Hepatic fat content
  - MRI-PDFF

NIT as RLSE: Search Strategy

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Databases	NIT Search Term (must include ≥1):	Disease Search Term (must include ≥1):	Study Design Search Term
• Pubmed (Medline, NIH) • Hepatology • EBSCO host • Science Direct (Elsivier) • NEJM • Sage Journals • The Lancet • Google Scholar	• VCTE • MRE • ELF • MRI-PDFF	• MASH • MASLD • NASH • NAFLD	• Meta-analysis • Systematic review • Prospective cohort • Diagnostic • Prognostic • Predictive • Treatment response

Process:

- Inquiry in database with listed search parameters
- Check for patient population, NIT used
- Prioritize more recent publications
- Review study citations, select studies that fall within listed parameters
- Rank study relevance based on: research design, cohort size, population criteria

Additional inquiries:

- EASL abstracts
- AASLD abstracts

2024, 2023, 2022

Check for recent studies of interest:

- LIVERAGE
- VOYAGE
- ESSENCE
- BALANCED
- HARMONY
- ENLIVEN
- REGENERATE
- MAESTRO-NASH, NAFLD
- NATIVE
- STELLAR

Summary of Literature Review (Manuscripts)

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Topic	Total NIT papers	Prognosis: Baseline +/- change NIT and LRE	Treatment: NIT changes
VCTE	24	12	12
MRE	13	9	7
ELF	23	5	18
MRI-PDFF	19	3*	16
ALL	**46**	**23**	**26**

* predict histologic changes

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Literature Review: VCTE

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Summary of Literature Review: VCTE

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Number of papers	
Prognosis: Baseline +/- change VCTE and LRE	**Treatment:** VCTE changes
12	12

N of patients	LRE endpoints	Percent with endpoints
27,684	1,360	4.9%

N of patients
6,295

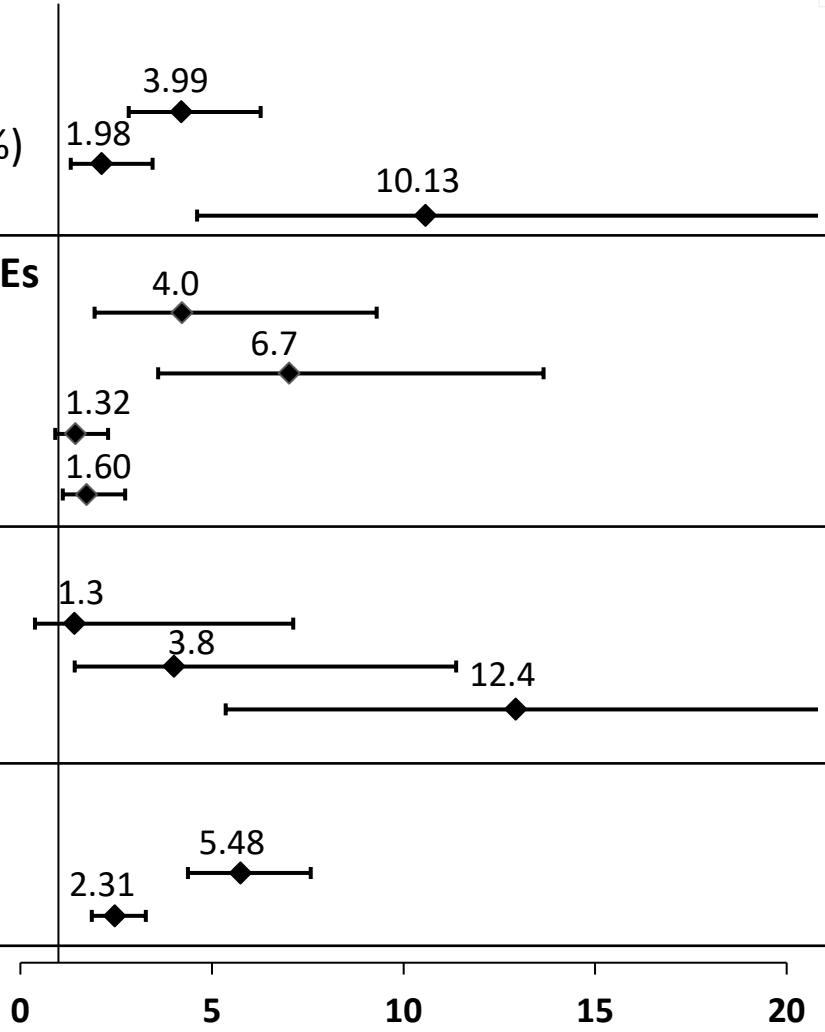
Prognosis: VCTE -AUROC/tAUC

Reference	Drug studied	AUROC/tAUC (95% CI) for VCTE-LSM	P value
Petta et al. (2021)	NA (N=533)	Prediction of liver decompensation	--
		Predicting liver-related death	--
		Predicting HCC	--
Lin et al. (2024)	NA (N=12,948)	**Prediction of LRE**	
		At 3 years	0.12
		At 5 years	0.003
		Prediction of hepatic decompensation	
		At 3 years	0.09
		At 5 years	< 0.001
Pennisi et al. (2023)	NA (N=614)	**In patients with biopsy-proven NAFLD**	< 0.001
		At 36 months	0.008
		At 60 months	0.006
		At 96 months	0.001

AUROC, Area under the receiver operating curve; CI, confidence interval; HCC, hepatocellular carcinoma; LRE, liver-related event; LSM, liver stiffness measurement; NA, not applicable/data not provided; NAFLD, non-alcoholic fatty liver disease; tAUC, ime-dependent receiver operating characteristic curve; VCTE, vibration-controlled transient elastography

Prognosis: VCTE- Hazard Ratio

Reference	Drug studied	HR/aHR (95% CI)	P value
Loomba et al. (2023)	Selonsertib/ simtuzumab (N=1,398)	**LS as a predictor of LREs** Baseline LS ≥16.6 kPa LS increase by ≥5kPa (and ≥20%) Baseline LS ≥30.7 kPa	 < 0.0001 0.008 < 0.0001
Gawrieh et al. (2024)	NA (N=1,403)	**LSM progression and risk of LREs** LSM ≥10 kPa LSM ≥15 kPa Increase in LSM by ≥30% kPa Increase in LSM by ≥50% kPa	 < 0.01 < 0.01 0.26 0.05
Bousier et al. (2022)	NA (N=1,057)	**Risk of LREs** FIB4 ≥ 1.30, VCTE <8.0 kPa FIB4 ≥ 1.30, VCTE 8.0-12.0 kPa FIB4 ≥ 1.30, VCTE >12.0 kPa	 -- -- --
Braude et al. (2023)	NA (N=6,341)	**LSM as predictor of mortality** LSM ≥10 kPa (univariate) LSM ≥10 kPa (multivariate)	 < 0.01 < 0.01



aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; LRE, liver-related event; LS, liver stiffness; LSM, liver stiffness measurement; NA, not applicable/data not provided; VCTE, vibration-controlled transient elastography

Prognosis: VCTE -Hazard Ratio

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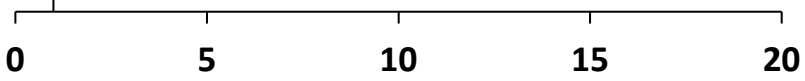
Reference	Drug studied	HR/aHR (95% CI)	P value
Shili-Masmoudi et al. (2020)	NA (N=2,245)	**LSM as a predictor of LREs** Baseline LSM	2.85 0.0002
Sanyal et al. (2022)	Selonsertib/ simtuzumab (N=1,135)	**LS as a predictor of LREs** 13%/2-kPa increase in LS	1.13 --
Johnson et al. (2022)	NA (N=243)	**LSM as a predictor of LREs** Per unit increase in LSM	1.07 < 0.001
Petta et al. (2021)	NA (N=533)	**Baseline LSM as predictor of** Hepatic decompensation HCC Liver-related mortality **Change in LSM as predictor of** Liver-related mortality Overall mortality HCC Hepatic decompensation	 1.03 1.03 1.02 1.96 1.73 1.72 1.56
			 < 0.01 0.003 0.005 0.02 0.01 0.04 0.04



aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event; LS, liver stiffness; LSM, liver stiffness measurement; NA, not applicable/data not provided; VCTE, vibration-controlled transient elastography

Prognosis: Baseline and Change in VCTE and LRE

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12 studies: 27,284 patients, 1,360 events

Baseline predicting LRE (n=12)

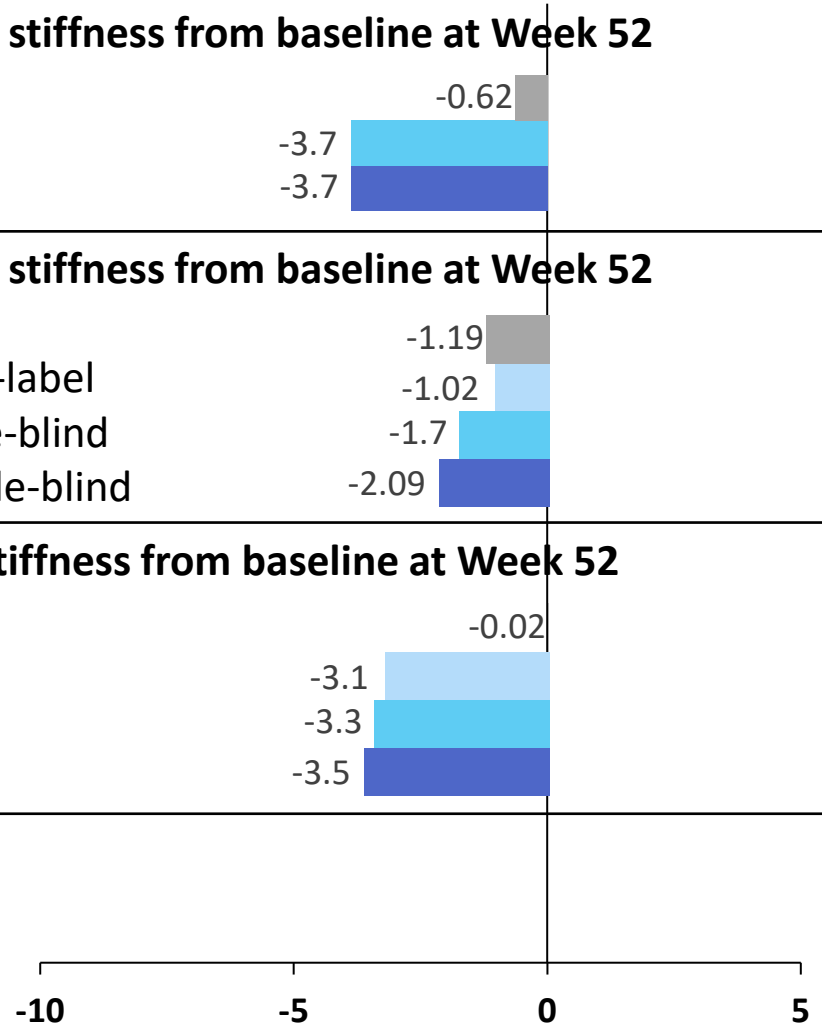
- All studies: LSM predicted LRE (or cirrhosis progression)
- Measures of model prediction (AUROC, tAUROC, C statistic) were mostly > 0.8
  - Not significantly different compared to histology (2 studies)
- HR predicting LRE ranged from 1.1 - > 10 (depend on cut point and analysis method

Change from base (n=5)

- Addition of serial LSM increased prediction
  - Exception is if include latest LSM in the model with base and previous values
- Stable LSM and low have the best prognosis
- LSM progression (however defined) are more likely to have LRE

Treatment: VCTE change with treatment

Reference	Drug studied	Change in liver stiffness as measured by VCTE	P value
Harrison et al. (2024)	Resmetirom or placebo (N=966)	**LS mean % change in liver stiffness from baseline at Week 52** Placebo Resmetirom 80 mg Resmetirom 100 mg	 -0.62 -3.7 -3.7	 --
Harrison et al. (2023)	Resmetirom or placebo (N=1,143)	**LS mean % change in liver stiffness from baseline at Week 52** Placebo Resmetirom 100 mg open-label Resmetirom 80 mg double-blind Resmetirom 100 mg double-blind	 -1.19 -1.02 -1.7 -2.09	 0.6614 0.1710
Loomba et al. (2024)	Tirzepatide or placebo (N=190)	**Absolute change in liver stiffness from baseline at Week 52** Placebo Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg	 -0.02 -3.1 -3.3 -3.5	 --



LS, least square; VCTE, vibration-controlled transient elastography

Treatment: VCTE change with treatment

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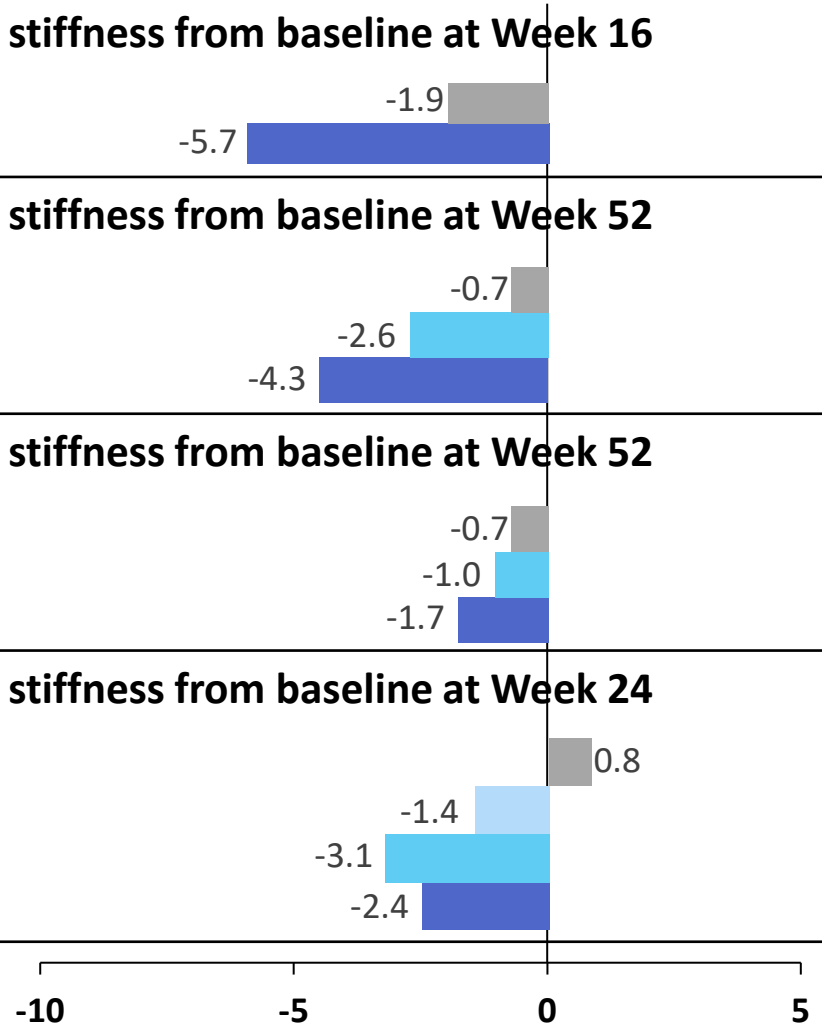
Reference	Drug studied	Change in liver stiffness as measured by VCTE	P value
Harrison et al. (2023)	Efruxifermin or placebo (N=30)	**LS mean % change in liver stiffness from baseline at Week 16** Placebo Efruxifermin 50 mg	< 0.01
Harrison et al. (2023)	Efruxifermin or placebo (N=128)	**LS mean % change in liver stiffness from baseline at Week 52** Placebo Efruxifermin 28 mg Efruxifermin 50 mg	< 0·01 < 0·01
Francque et al. (2021)	Lanifibranor or placebo (N=247)	**LS mean % change in liver stiffness from baseline at Week 52** Placebo Lanifibranor 800 mg Lanifibranor 1200 mg	--
Loomba et al. (2023)	Pegozafermin or placebo (N=222)	**LS mean % change in liver stiffness from baseline at Week 24** Placebo Pegozafermin 15 mg Pegozafermin 30 mg Pegozafermin 44 mg	--



LS, least square; VCTE, vibration-controlled transient elastography

Treatment: VCTE change with treatment

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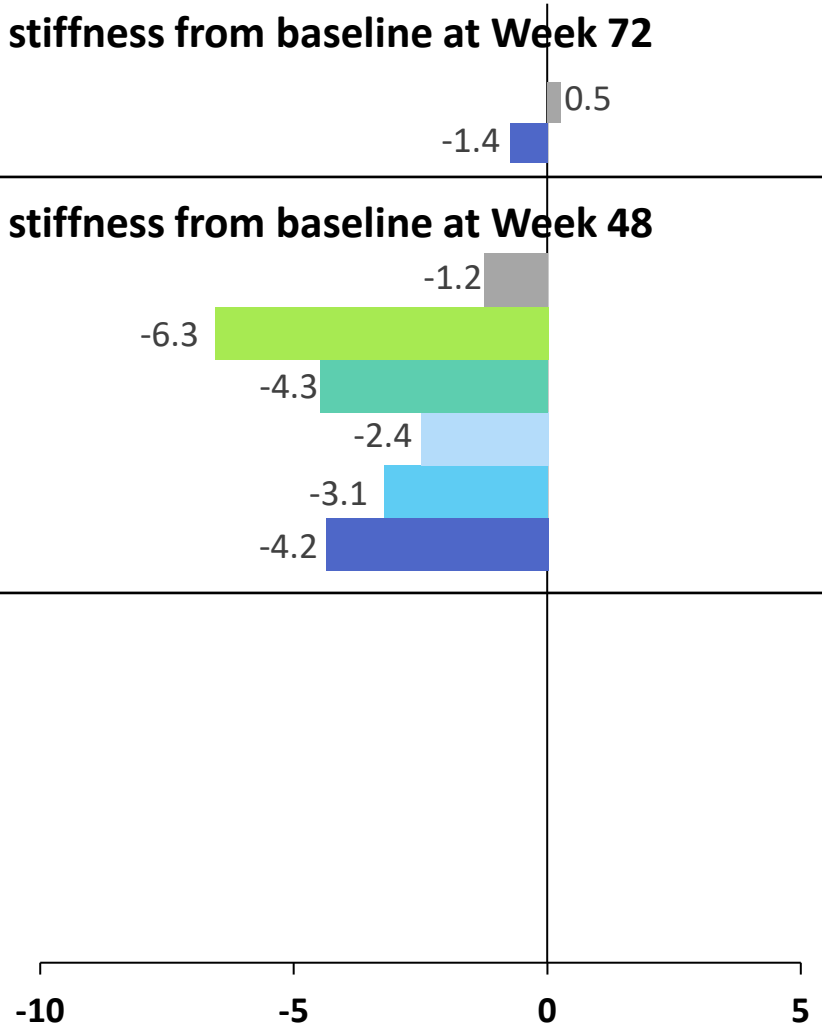
Reference	Drug studied	Change in liver stiffness as measured by VCTE	P value
Okanoue et al. (2021)	Apararenone or placebo (N=47)	**LS mean % change in liver stiffness from baseline at Week 72** Placebo Apararenone 10 mg	 -- --
Loomba et al. (2021)	Firsocostat, Cilofexor, Selonsertib, or placebo (N=392)	**LS mean % change in liver stiffness from baseline at Week 48** Placebo Firsocostat Cilofexor Firsocostat/Selonsertib Cilofexor/Selonsertib Cilofexor/Firsocostat	 -1.2 -6.3 -4.3 -2.4 -3.1 -4.2	 0.021 0.16 0.50 0.31 0.10



LS, least square; VCTE, vibration-controlled transient elastography

Treatment: VCTE change with treatment

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12 studies: 6,295 patients

- Analysis
  - Mean change from baseline or 25 or 30% reduction
- In studies of a drug without activity (e.g. selonsertib)
  - No difference between treated and placebo
  - No association between histologic response and LSM
- In studies of active drugs
  - LSM differences demonstrated between treated and placebo patients (numerically or statistically)
    - LSM changes are sensitive: some studies with small numbers (30-50) show a trend or statistical difference and dose response
    - LSM changes parallel changes in other NIT
    - Some studies statistical testing not done
    - Lack of statistical significance may be analysis dependent (mean change vs responder)

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Literature Review: MRE

Berkeley Public Health

Summary of Literature Review: MRE

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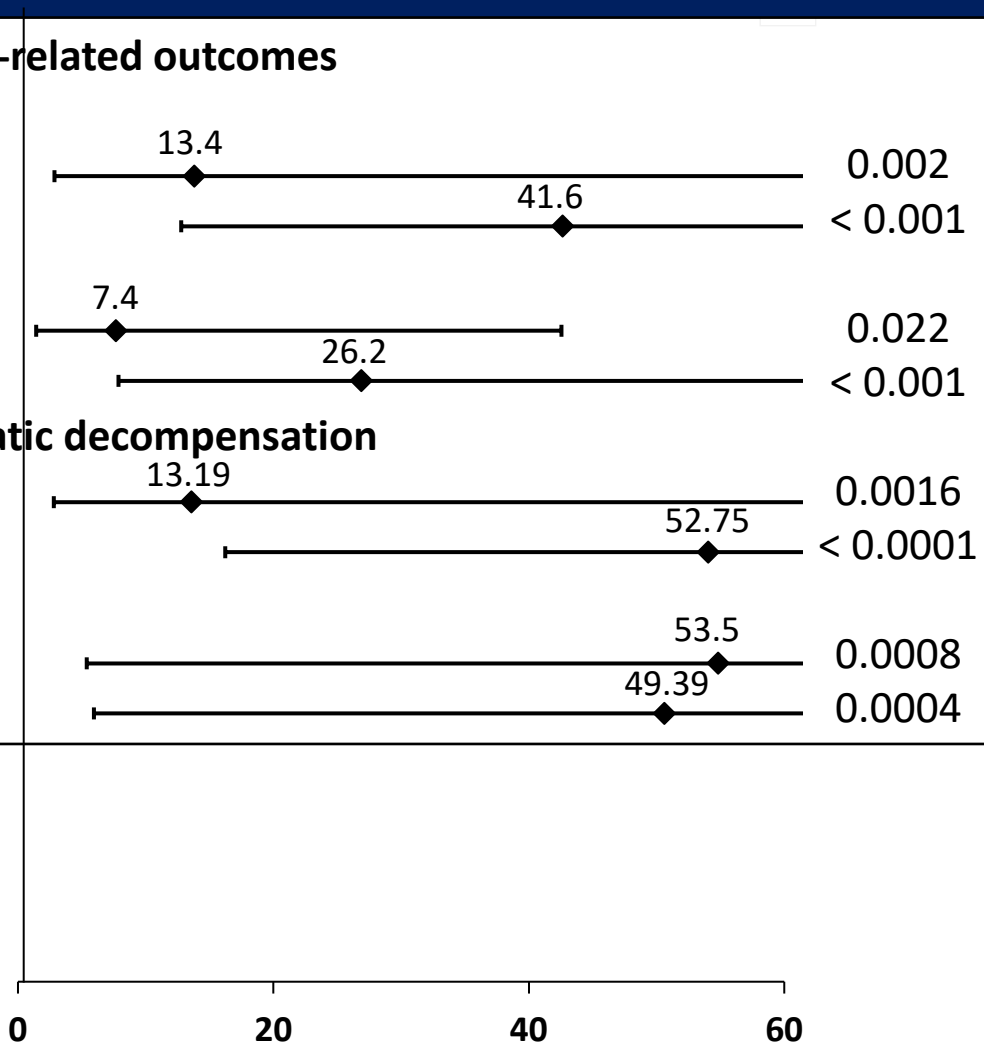
Number of papers	
Prognosis: Baseline +/- change MRE and LRE	**Treatment:** MRE changes
9	7

N of patients	LRE endpoints	Percent with endpoints
5,056	525	10.0%

N of patients
2,995

Prognosis: MRE- odds ratio

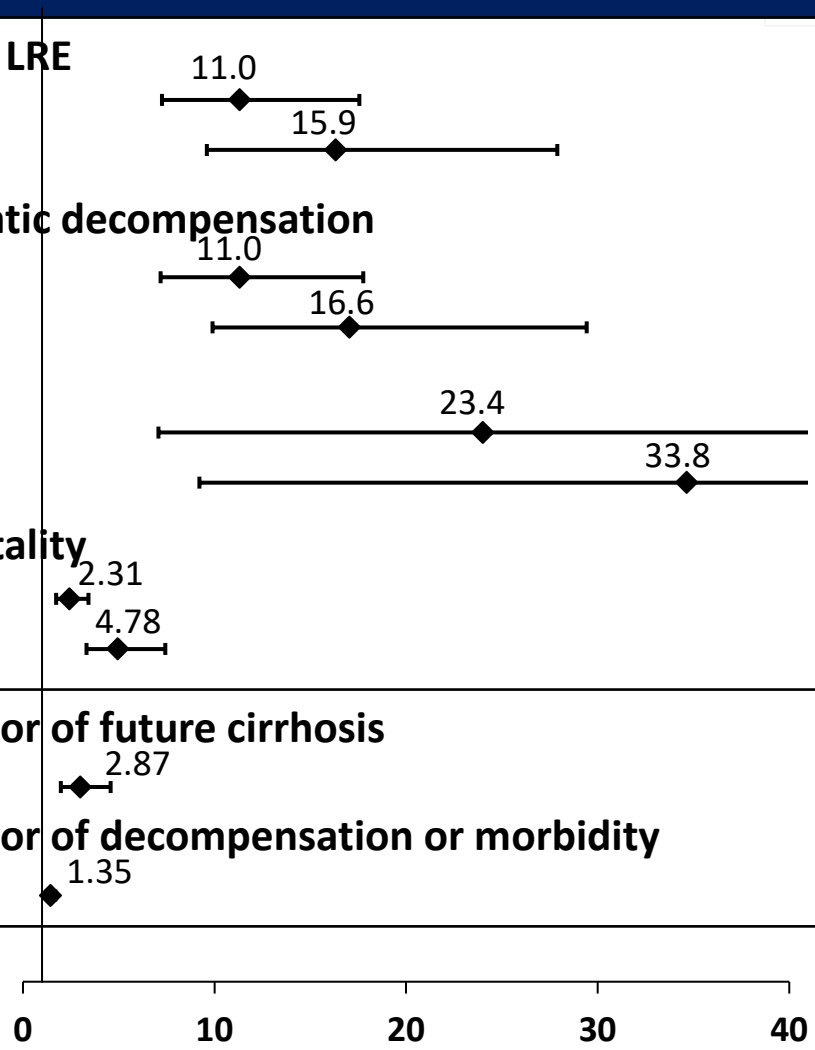
Reference	N	OR (95% CI)	P value
		Higher LSM by MRE as a predictor of liver-related outcomes	
		Univariate analysis	
		LSM with MRE of 3.63–5.0 kPa	0.002
		LSM with MRE of >5 kPa	< 0.001
		Multivariate analysis	
		LSM with MRE of 3.63–5.0 kPa	0.022
Ajmera et al. (2022)	265	LSM with MRE of >5 kPa	< 0.001
		Higher LSM by MRE as a predictor of hepatic decompensation	
		LSM with MRE of 3.63–5.0 kPa	0.0016
		LSM with MRE of >5 kPa	< 0.0001
		Higher LSM by MRE as a predictor of HCC	
		LSM with MRE of 3.63–5.0 kPa	0.0008
		LSM with MRE of >5 kPa	0.0004



CI, confidence interval; HCC, hepatocellular carcinoma; LRE, liver-related event; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NA, not applicable/data not provided; OR, odds ratio

Prognosis: MRE- Hazard Ratio

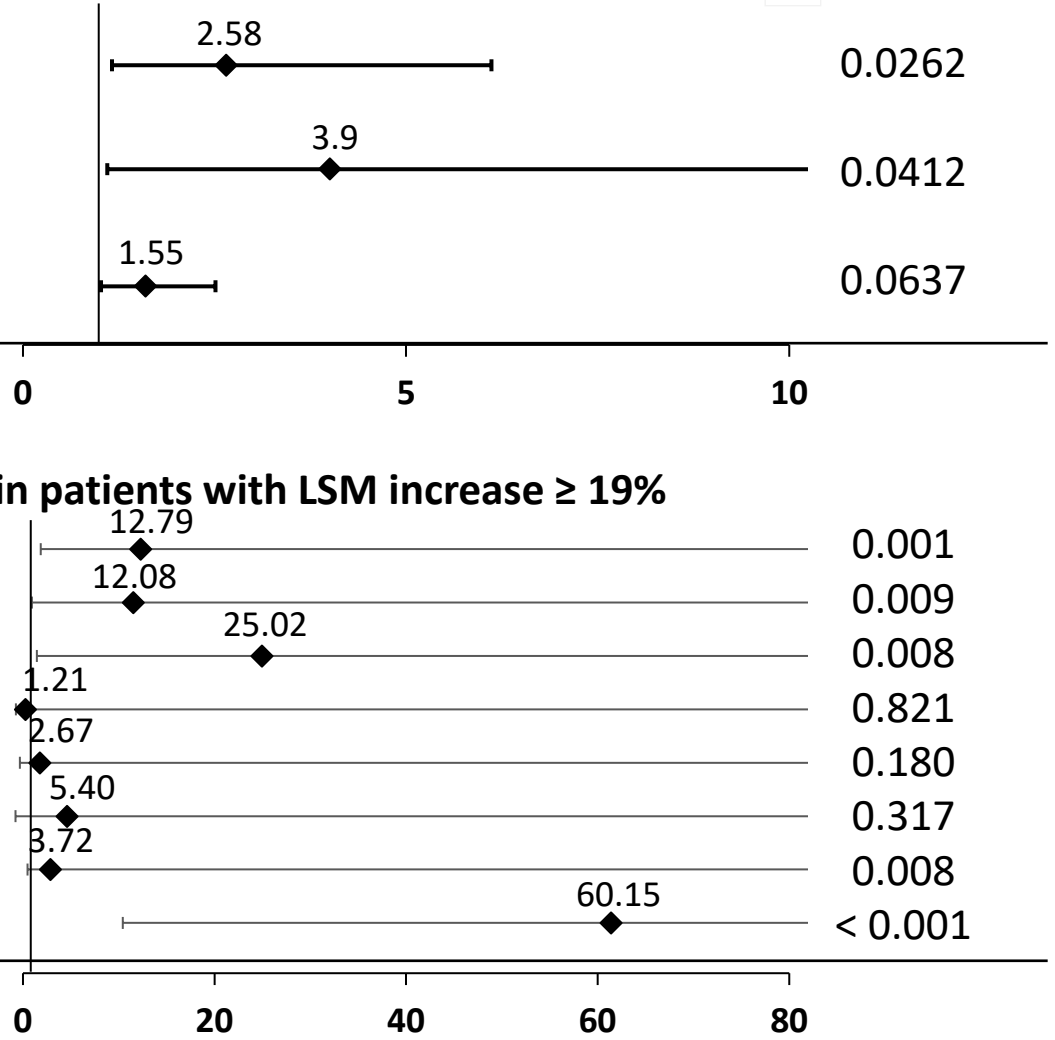
Reference	Drug studied	HR/aHR (95% CI)	P value
Ajmera et al. (2022)	NA (N=2,018)	**MRE as a predictor of progress to LRE**	
		MRE 5–8 kPa	< 0.001
		MRE ≥ 8 kPa	< 0.001
		MRE as a predictor of risk of hepatic decompensation	
		MRE 5–8 kPa	< 0.001
		MRE ≥ 8 kPa	< 0.001
		MRE as a predictor of risk of HCC	
		MRE 5–8 kPa	< 0.001
		MRE ≥ 8 kPa	< 0.001
		MRE as a predictor of risk of mortality	
		MRE 5–8 kPa	< 0.001
		MRE ≥ 8 kPa	< 0.001
Gidener et al. (2021)	NA (N=829)	**Baseline LSM by MRE as a predictor of future cirrhosis**	
		Per one kPa increase	< 0.0001
		Baseline LSM by MRE as a predictor of decompensation or morbidity	
		Per one kPa increase	0.0002



aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NA, not applicable/data not provided

Prognosis: MRE- Hazard Ratio

Reference	Drug studied	HR/aHR (95% CI)	P value
Kim et al. (2024)	NA (N=1,254)	MRE as a predictor of risk of hepatic decompensation	0.0262
		MRE as a predictor of risk of HCC	0.0412
		MRE as a predictor of risk of all-cause mortality	0.0637
Tobayashi et al. (2023)	NA (N=405)	**Relative risk of clinical outcomes in patients with LSM increase ≥ 19%**	
		LRE	0.001
		Decompensated cirrhosis	0.009
		HCC	0.008
		Overall mortality	0.821
		Extrahepatic malignancies	0.180
		Cardiovascular events	0.317
		Overall events	0.008
		New onset of cirrhosis (n=386)	< 0.001



aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NA, not applicable/data not provided

Prognosis: Baseline and Change in MRE and LRE

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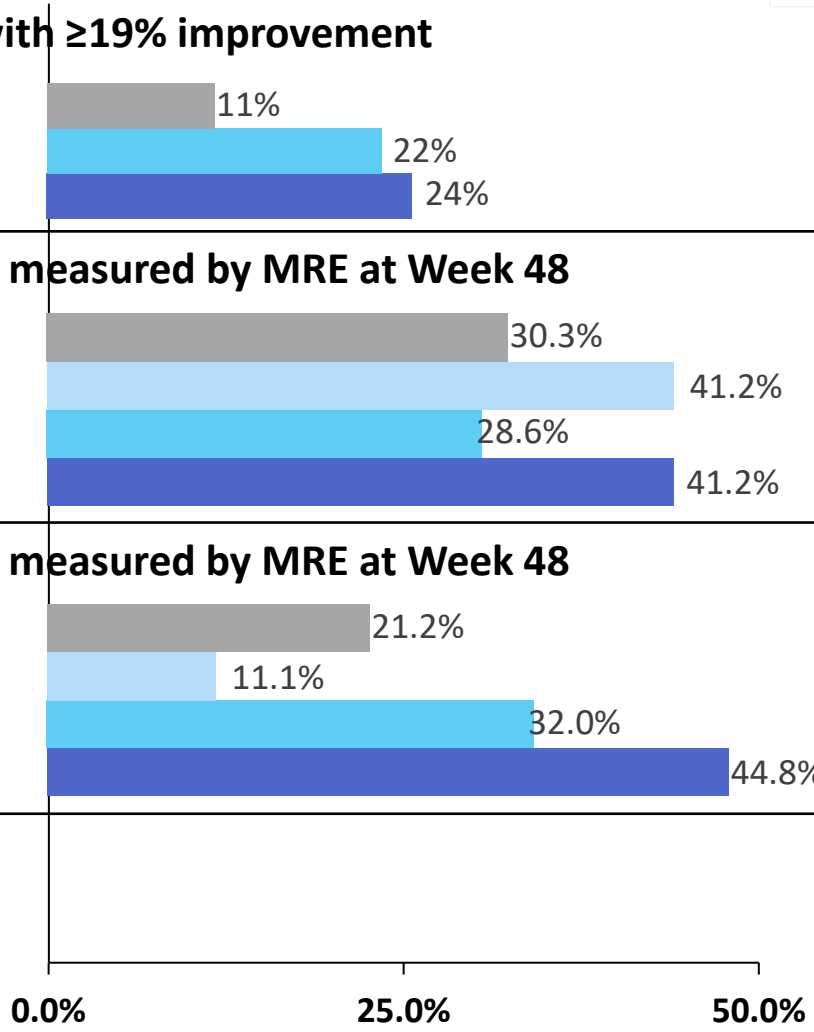
9 studies: 5,064 patients, 513 events

- Overall fewer studies
- Baseline MRE solid predicted of LRE (or cirrhosis progression)
- At least 1 study demonstrates association of base + change in MRE and LRE

Treatment: MRE change with treatment

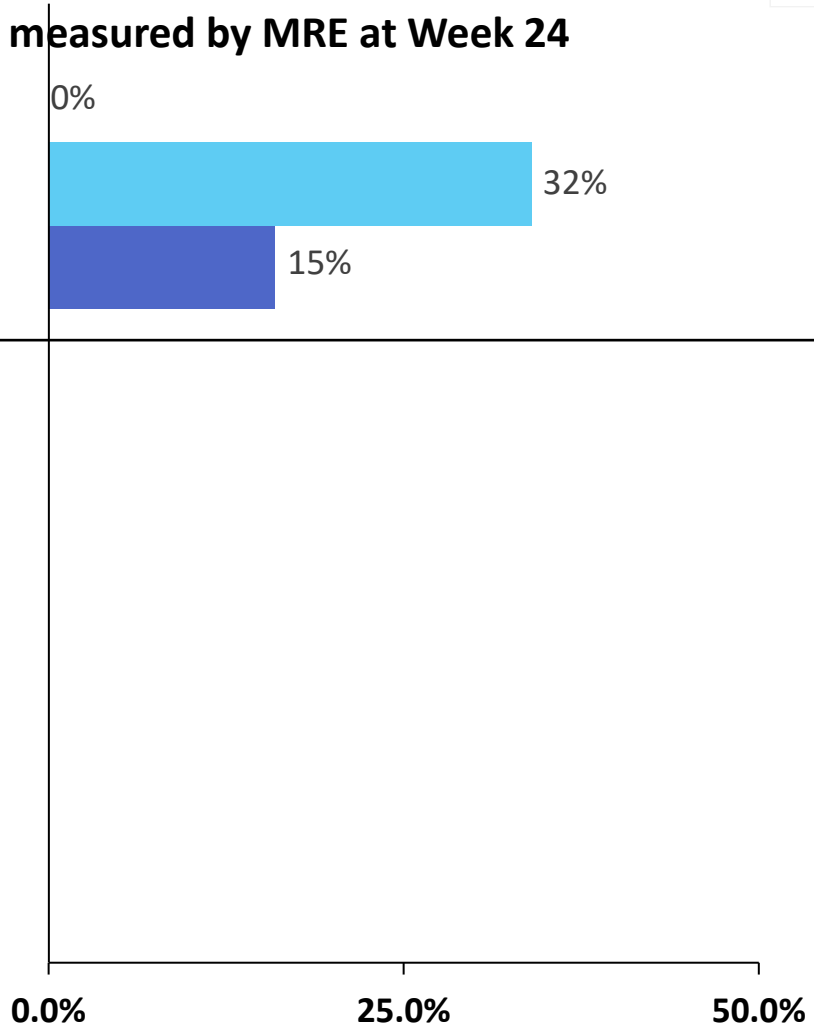
Reference	Drug studied	Change in MRE score	P value
Harrison et al. (2023)	Resmetirom or placebo (N=972)	**Percentage of paired MREs with ≥19% improvement** Placebo Resmetirom 80 mg DB Resmetirom 100 mg OL/DB	--
Loomba et al. (2024)	Pegbelfermin or placebo (N=197)	**≥15% relative reduction in LS measured by MRE at Week 48** Placebo Pegbelfermin 10 mg Pegbelfermin 20 mg Pegbelfermin 40 mg	 0.412 0.853 0.426
Abdelmalek et al. (2024)	Pegbelfermin or placebo (N=154)	**≥15% relative reduction in LS measured by MRE at Week 48** Placebo Pegbelfermin 10 mg Pegbelfermin 20 mg Pegbelfermin 40 mg	 0.329 0.374 0.051



DB, double-blind; LS, liver stiffness; MRE, magnetic resonance elastography; OL, open-label

Treatment: MRE change with treatment

Reference	Drug studied	Change in MRE score	P value
Loomba et al. (2018)	Selonsertib and/or Simtuzumab (N=72)	**≥15% relative reduction in LS measured by MRE at Week 24** Simtuzumab Selonsertib 6 mg ± Simtuzumab Selonsertib 18 mg ± Simtuzumab	--



LS, liver stiffness; MRE, magnetic resonance elastography

Treatment: MRE change with treatment

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7 studies: 2,995 patients

- Analysis
  - Mean change from baseline or 15-19% reduction from baseline
- Often a subgroup of larger studies so statistical testing is limited by sample size
- Although numerically in right direction (to show treatment effect), no study with significant change in MRE between treated and placebo

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Literature Review: ELF

Berkeley Public Health

Summary of Literature Review: ELF

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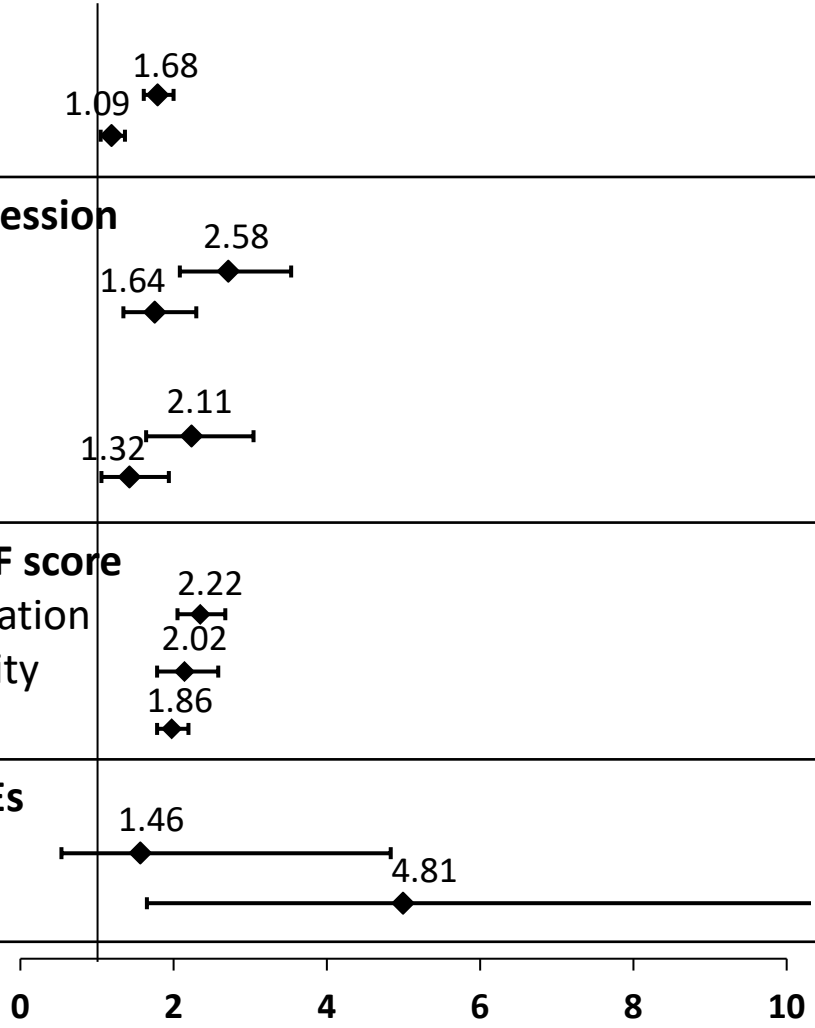
Number of papers	
Prognosis: Baseline +/- change ELF and LRE	**Treatment:** ELF changes
5	18

N of patients	LRE endpoints	Percent with endpoints
3,342	221	6.6%

N of patients
7,090

Prognosis: ELF- Hazard Ratio

Reference	Drug studied		HR/aHR (95% CI)	P value
Sanyal et al. (2022)	Simtuzumab and selonsertib (N=1,135)	**ELF as a predictor for LREs**		
		Baseline ELF, per 0.5 units	1.68 (1.09)	< 0.0001
		Change in ELF, per 0.5 units		0.2274
Sanyal et al. (2019)	Simtuzumab (N=475)	**ELF predictor of cirrhosis progression**		
		Higher baseline ELF	2.58 (1.64)	< 0.001
		Greater change ELF		< 0.001
		ELF as predictor of LREs		
		Baseline ELF	2.11 (1.32)	< 0.001
		Change from baseline in ELF		0.09
Pearson et al. (2024)	NA (N=1,327)	**With per unit change in the ELF score**		
		Increase in hepatic decompensation	2.22	--
		Increase in liver-related mortality	2.02	--
		Increase in all-cause mortality	1.86	--
Are et al. (2021)	Belapectin (N=161)	**ELF score as a predictor for LREs**		
		ELF score 9.8 to 11.2	1.46	--
		ELF score of 11.3	4.81	--



aHR, adjusted hazards ration; CI, confidence interval; ELF, enhanced liver fibrosis; HR, hazards ratio; LRE, liver-related event; NA, not applicable/data not provided

Prognosis: Baseline and Change in ELF and LRE

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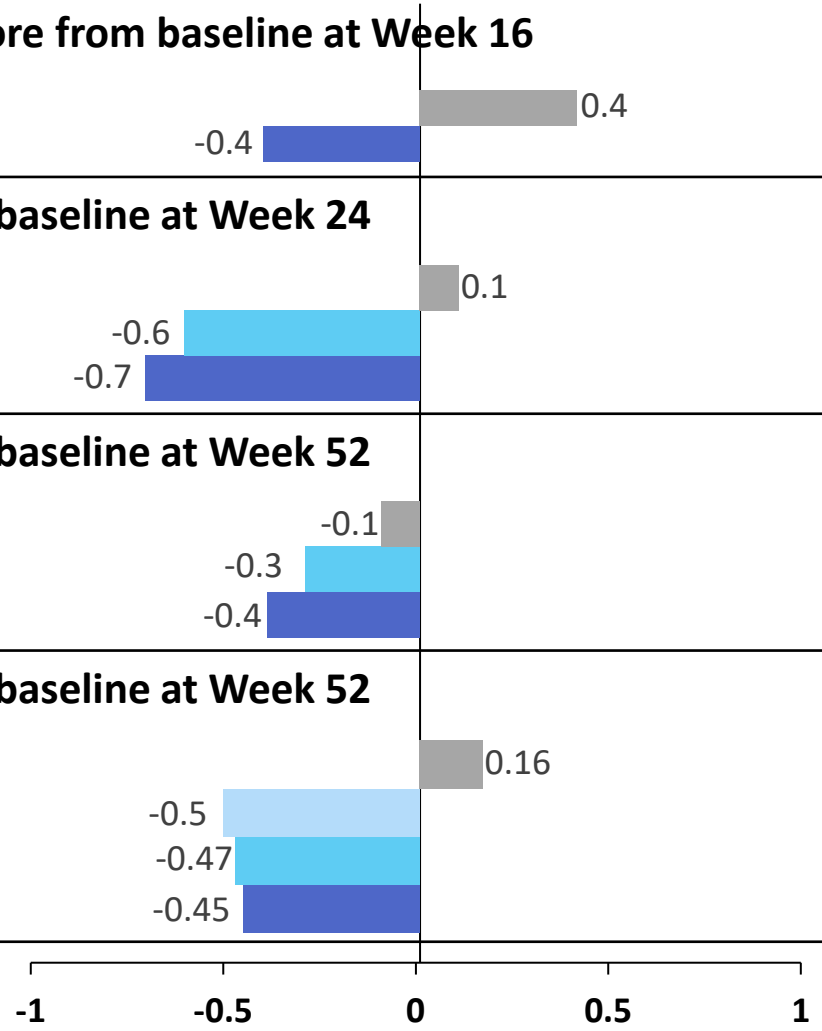
5 studies: 3,342 patients, 221 events

Baseline or change in ELF predicting LRE

- Overall fewer studies
- For most studies baseline ELF predicted LRE (or progression to cirrhosis)
- Base ELF associated with progression to cirrhosis and LRE, while change in ELF associated with progression to cirrhosis in STELLAR studies

Treatment: ELF change with treatment

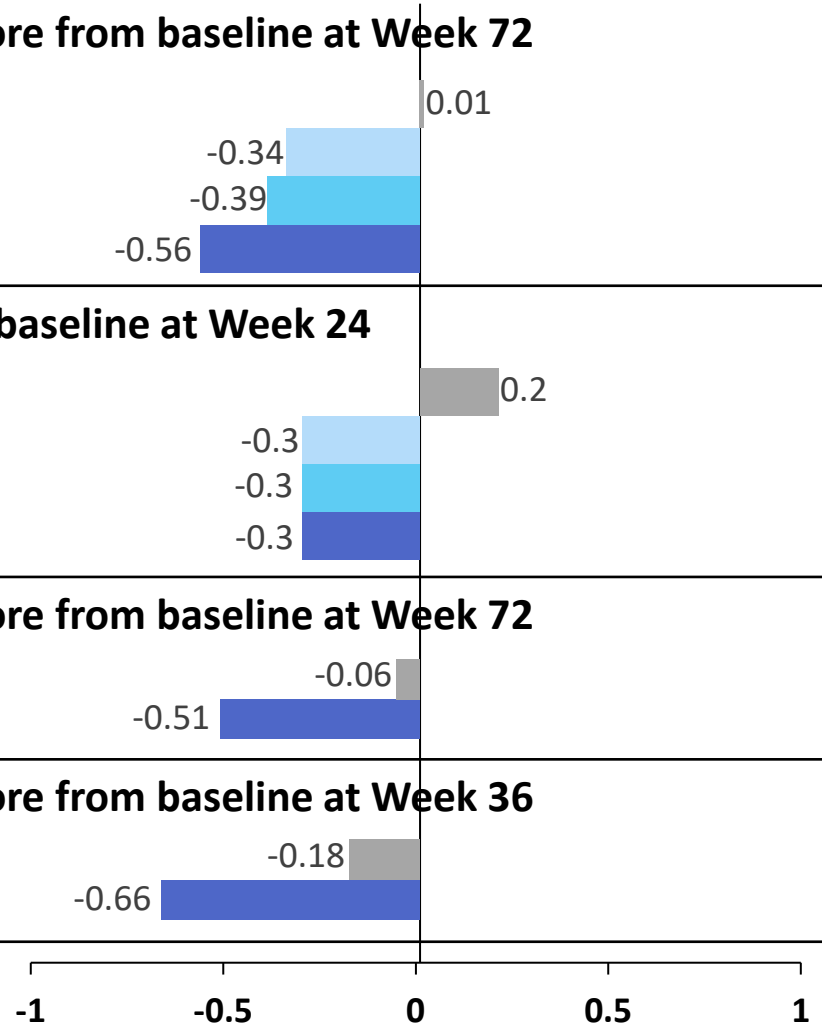
Reference	Drug studied	Change in ELF score	P value
Harrison et al. (2023)	Efruxifermin or placebo (N=30)	**LS mean change in ELF score from baseline at Week 16** Placebo Efruxifermin 50 mg	 0.4 -0.4 0.0036
Harrison et al. (2023)	Efruxifermin or placebo (N=128)	**Change in ELF score from baseline at Week 24** Placebo Efruxifermin 28 mg Efruxifermin 50 mg	 0.1 -0.6 -0.7 < 0·001 < 0·001
Harrison et al. (2024)	Resmetirom or placebo (N=966)	**Change in ELF score from baseline at Week 52** Placebo Resmetirom 80 mg Resmetirom 100 mg	 -0.1 -0.3 -0.4 --
Loomba et al. (2024)	Tirzepatide or placebo (N=190)	**Change in ELF score from baseline at Week 52** Placebo Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg	 0.16 -0.5 -0.47 -0.45 --



ELF, enhanced liver fibrosis; LS, least square

Treatment: ELF change with treatment

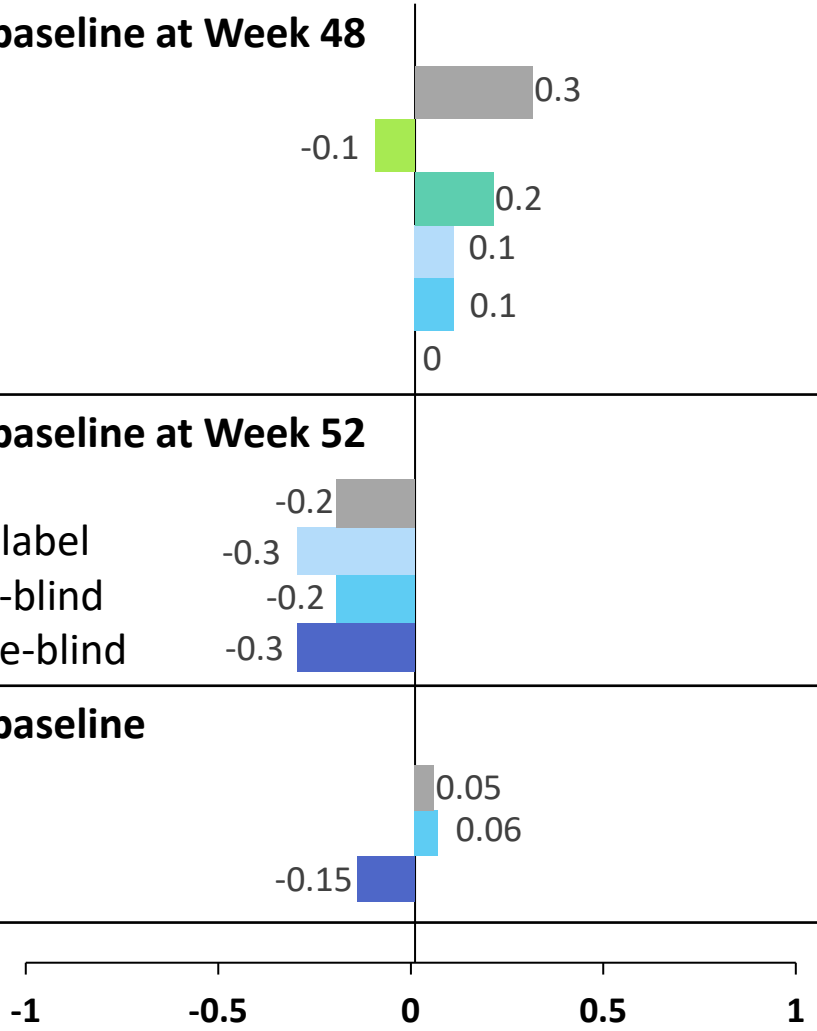
Reference	Drug studied	Change in ELF score	P value
Newsome et al. (2021)	Semaglutide or placebo (N=320)	**LS mean change in ELF score from baseline at Week 72** Placebo Semaglutide 0.1 mg Semaglutide 0.2 mg Semaglutide 0.4 mg	--
Loomba et al. (2023)	Pegozafermin or placebo (N=222)	**Change in ELF score from baseline at Week 24** Placebo Pegozafermin 15 mg Pegozafermin 30 mg Pegozafermin 44 mg	--
Okanoue et al. (2021)	Apararenone or placebo (N=47)	**LS mean change in ELF score from baseline at Week 72** Placebo Apararenone 10 mg	0.027
Harrison et al. (2019)	Resmetirom or placebo (N=125)	**LS mean change in ELF score from baseline at Week 36** Placebo Tirzepatide 5 mg	0.017



ELF, enhanced liver fibrosis; LS, least square

Treatment: ELF change with treatment

Reference	Drug studied	Change in ELF score	P value
Loomba et al. (2021)	Firsocostat, Cilofexor, Selonsertib, or placebo (N=392)	**Change in ELF score from baseline at Week 48** Placebo Firsocostat Cilofexor Firsocostat/Selonsertib Cilofexor/Selonsertib Cilofexor/Firsocostat	 -- 0.010 0.34 0.074 0.14 0.024
Harrison et al. (2023)	Resmetirom or placebo (N=1,143)	**Change in ELF score from baseline at Week 52** Placebo Resmetirom 100 mg open-label Resmetirom 80 mg double-blind Resmetirom 100 mg double-blind	 0.84 0.60
Shankar et al. (2024)	Cotadutide or placebo (N=74)	**Change in ELF score from baseline** Placebo Cotadutide 300 µg Cotadutide 600 µg	 --



ELF, enhanced liver fibrosis

Treatment: ELF change with treatment

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18 studies: 7,090 patients

- Analysis
  - Mean change from baseline
- In studies of a drug without activity (e.g. selonsertib)
  - No difference between treated and placebo
  - No association between histologic response and ELF
- In studies of active drugs
  - Very robust data
  - ELF differences demonstrated between treated and placebo patients (numerically or statistically)
    - ELF changes are sensitive: some studies with small numbers (30-50) show a trend or statistical difference and dose response
    - ELF changes parallel changes in other NIT
    - Some studies statistical testing not done
    - Lack of statistical significance may be analysis (mean change vs responder) or drug mechanism dependent (time course too short to show fibrosis difference)

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Literature Review: MRI-PDFF

Berkeley Public Health

Summary of Literature Review: MRI-PDFF

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Number of papers	
Prognosis: Baseline +/- change PDFF and LRE	**Treatment:** PDFF changes
3	16

N of patients	LRE endpoints	Percent with endpoints
576	0	0

N of patients
4,228

Prediction of Histologic Response: MRI-PDFF

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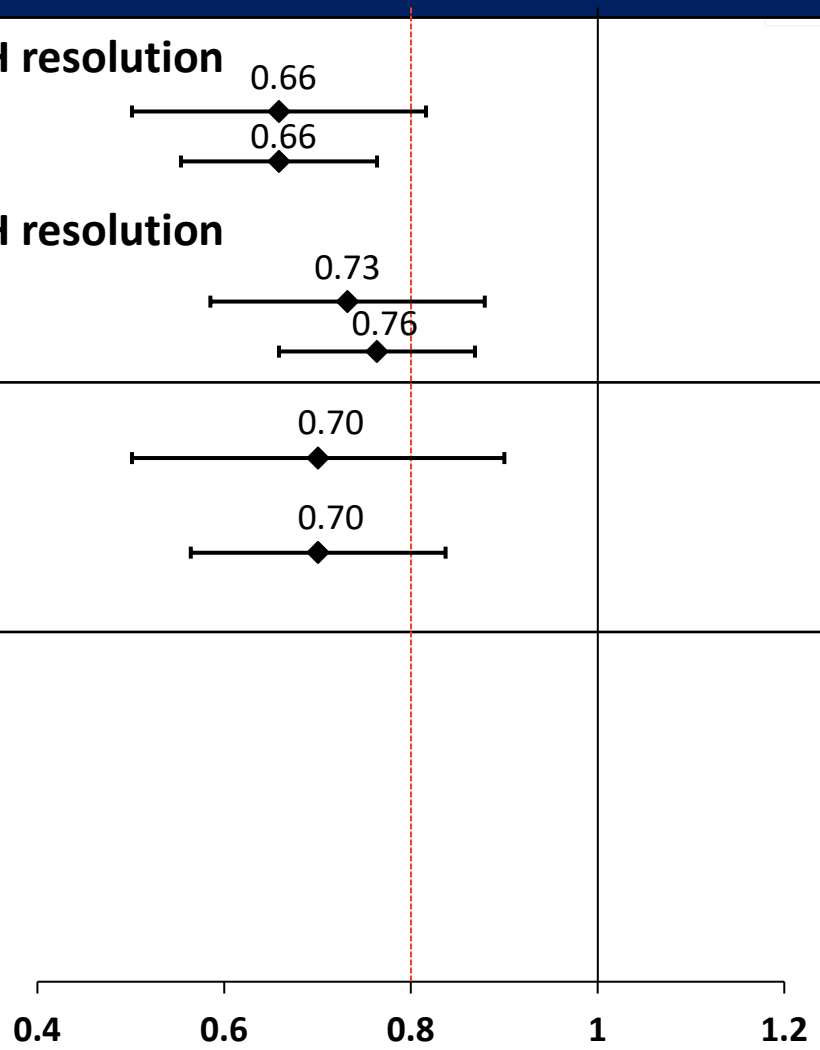
Reference	Drug studied	AUROC/tAUC (95% CI)	P value
Loomba et al. (2024)	NA (N=258)	**AUROC MRI-PDFF predict MASH resolution**	
		Derivation cohort (n=95) 0.66	0.005
		Validation cohort (n=163) 0.66	< 0.001
		AUROC MRI-PDFF predict MASH resolution	
		Derivation cohort (n=95) 0.73	0.06
		Validation cohort (n=163) 0.76	0.05
Jayakumar et al. (2019)	Selonsertib or simtuzumab (N=65)	AUROC of MRI-PDFF to predict NAS response 0.70	0.08
		AUROC of MRI-PDFF to predict steatosis response 0.70	0.014



AUROC, Area under the receiver operating curve; CI, confidence interval; MRI-PDFF, magnetic resonance imaging-derived measurements of proton density fat fraction; NAS, non-alcoholic fatty liver disease activity score; tAUC, time-dependent receiver operating characteristic curve/area under curve

Prognosis: Baseline and Change in MRI-PDFF and Mash resolution

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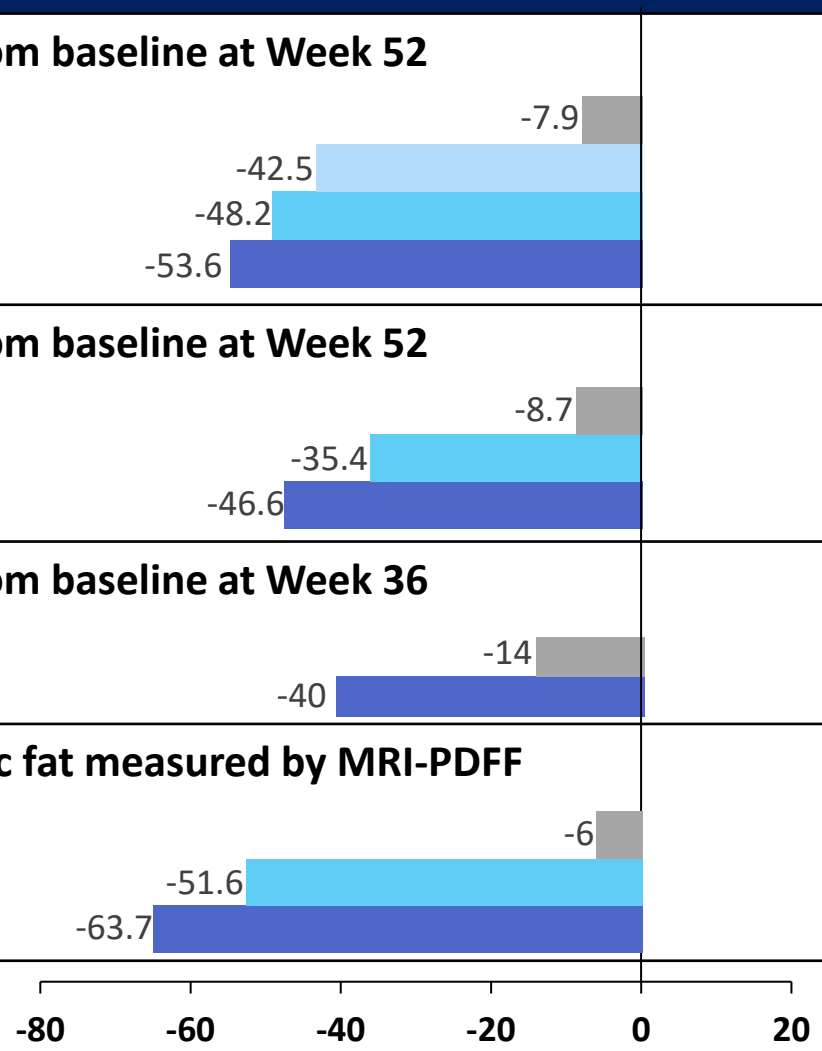
3 studies: 576 patients, 0 events

- Overall fewer studies
- No data on baseline or change in MRI-PDFF and LRE
- MRI-PDFF tracks changes in histologic steatosis

Treatment: MRI-PDFF change with treatment

Reference	Drug studied	% Change in hepatic fat measured by MRI-PDFF	P value
Harrison et al. (2023)	Resmetirom or placebo (N=1,143)	**% Change in MRI-PDFF from baseline at Week 52** Placebo Resmetirom 80 mg DB Resmetirom 100 mg DB Resmetirom 100 mg OL	 < 0.0001 < 0.0001 < 0.0001
Harrison et al. (2024)	Resmetirom or placebo (N=966)	**% Change in MRI-PDFF from baseline at Week 52** Placebo Resmetirom 80 mg Resmetirom 100 mg	 --
Harrison et al. (2019)	Resmetirom or placebo (N=348)	**% Change in MRI-PDFF from baseline at Week 36** Placebo Resmetirom 80 mg	 --
Harrison et al. (2023)	Efruxifermin or placebo (N=128)	**LS mean change in hepatic fat measured by MRI-PDFF** Placebo Efruxifermin 28 mg Efruxifermin 50 mg	 < 0.0001 < 0.0001



LS, least square; MRI-PDFF, magnetic resonance imaging-derived measurements of proton density fat fraction

Treatment: MRI-PDFF change with treatment

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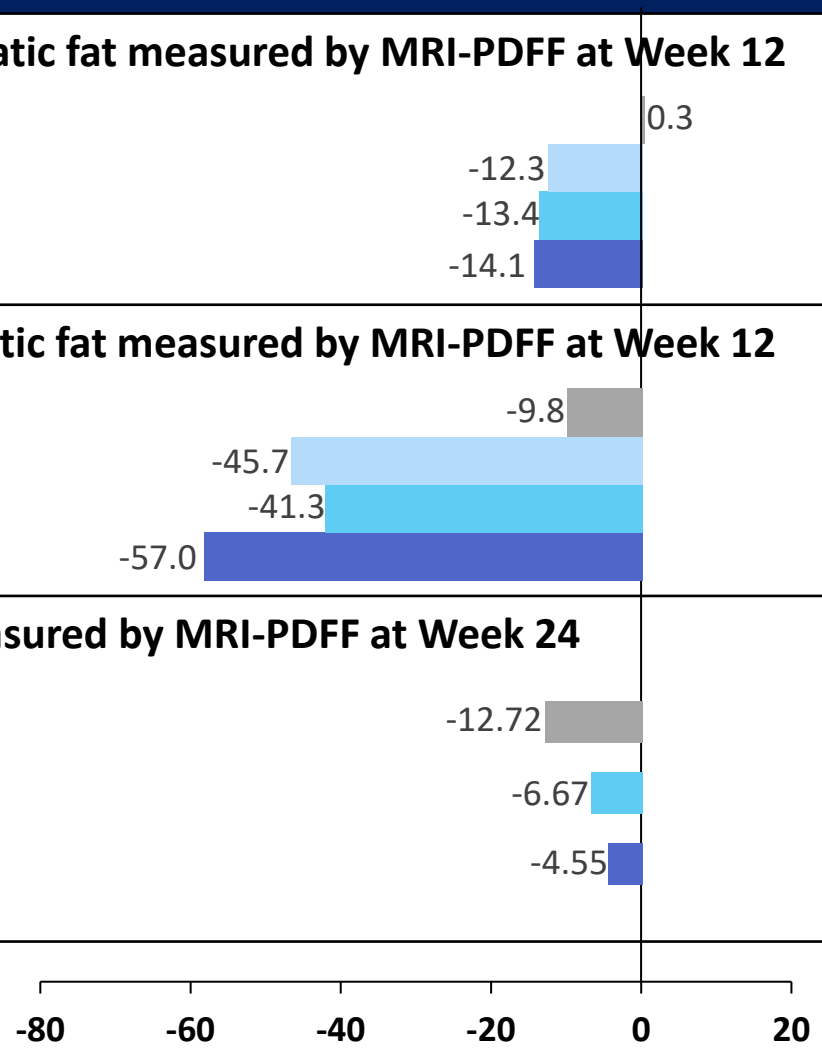
Reference	Drug studied	% Change in hepatic fat measured by MRI-PDFF	P value
Harrison et al. (2023)	Efruxifermin or placebo (N=80)	**LS mean % change in hepatic fat measured by MRI-PDFF at Week 12** Placebo Efruxifermin 28 mg Efruxifermin 50 mg Efruxifermin 70 mg	 < 0.0001 < 0.0001 < 0.0001
Loomba et al. (2024)	Tirzepatide or placebo (N=190)	**LS mean %change in hepatic fat measured by MRI-PDFF at Week 12** Placebo Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg	 --
Loomba et al. (2018)	Selonsertib or Simtuzumab (N=72)	**Change in hepatic fat measured by MRI-PDFF at Week 24** Simtuzumab Selonsertib 6 mg ± Simtuzumab Selonsertib 18 mg ± Simtuzumab	 --



LS, least square; MRI-PDFF, magnetic resonance imaging-derived measurements of proton density fat fraction

Treatment: MRI-PDFF change with treatment

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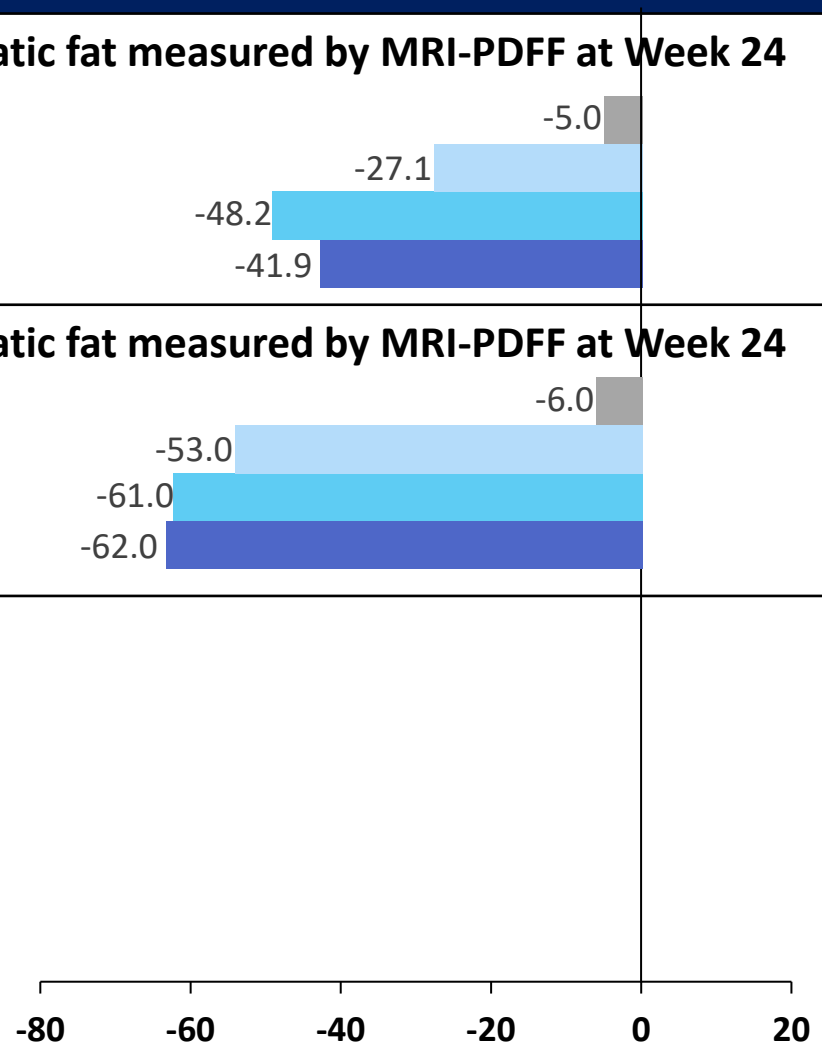
Reference	Drug studied	% Change in hepatic fat measured by MRI-PDFF	P value
Loomba et al. (2023)	Pegozafermin or placebo (N=222)	**LS mean % change in hepatic fat measured by MRI-PDFF at Week 24** Placebo Pegozafermin 15 mg Pegozafermin 30 mg Pegozafermin 44 mg	 < 0.0001 < 0.0001 < 0.0001
Sanyal et al. (2024)	Survodutide or placebo (N=293)	**LS mean % change in hepatic fat measured by MRI-PDFF at Week 24** Placebo Survodutide 2.4 mg Survodutide 4.8 mg Survodutide 6 mg	 --



LS, least square; MRI-PDFF, magnetic resonance imaging-derived measurements of proton density fat fraction

Treatment: MRI-PDFF change with treatment

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16 studies: 4,228 patients

- Analysis
  - Mean change from baseline, percent change from baseline, 15 or 30% reduction from baseline
- Sensitive marker to steatosis changes
- Large treatment effect detected compared to placebo
- Larger differences seen in MRI-PDFF than with fibrosis markers for some drugs (e.g., resmitirom)