Quantitative Imaging Biomarkers Alliance

RSNA

A Meta-Analysis on repeatability of Magnetic Resonance Elastography of Liver.

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Diagnosis of Liver Fibrosis

- Currently, liver biopsy is the "gold" standard
  - However, it's an imperfect "gold" standard

- Painful
- Complications (~0.5%) [1]
- Sampling error ~15-25% (only ~1/5,000th of liver mass obtained - <0.02% of the 1.5 kg liver)
- Sedation/GA
- Typically 24 hr. inpatient observation
- Substantial variability in staging of fibrosis (discordance in up to 33% of cases) [2]
- ~20% of specimens understaged [3]

[1] Martinez S, et al. Hepatology 2011l53:325-35
[2] Regev A, et al. AJG 2002;97:2614-2618
[3] Bedossa P, et al. Hepatology 2003;38:1449-1457

Diagnosis of Liver Fibrosis

- Currently, liver biopsy is the “gold” standard
  - However, it’s an imperfect “gold” standard

Hence:

Non-invasive techniques for assessment and quantification of liver fibrosis are critical for clinical surveillance and validation.

[1] Martinez S, et al. Hepatology 2011l53:325-35
[2] Regev A, et al. AJG 2002;97:2614-2618
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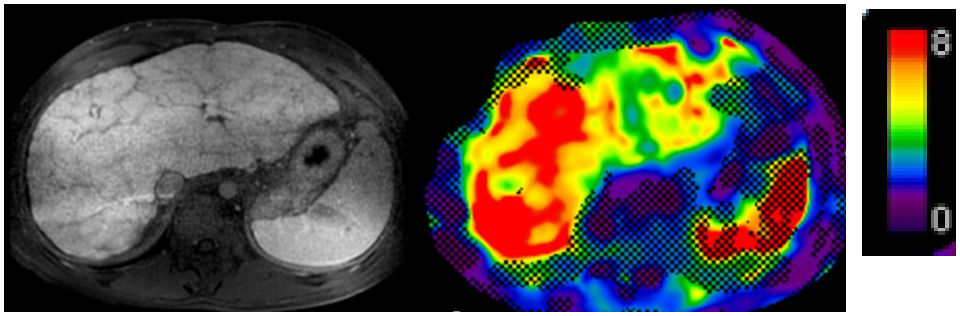
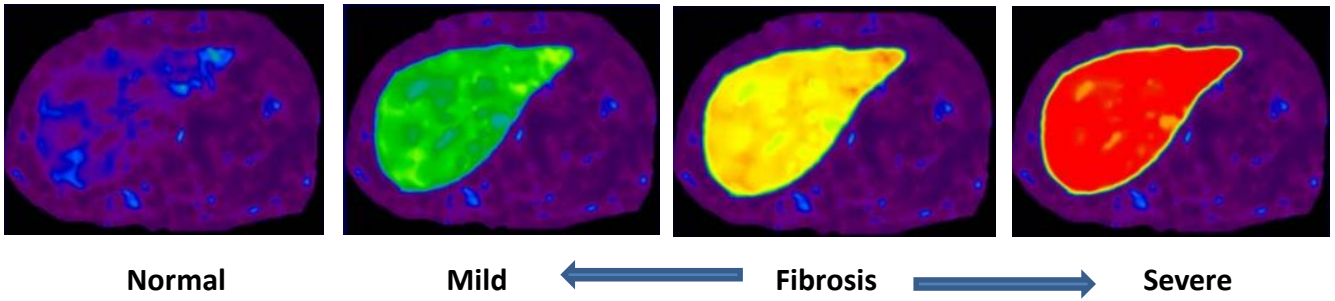
MR Elastography

Quantitative Imaging of Tissue Stiffness

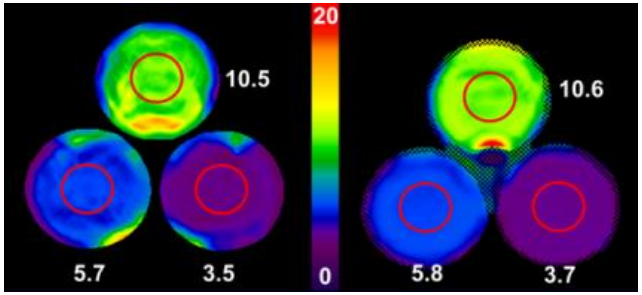


- Main application: Assessing liver fibrosis (Diagnosis, Surveillance and Therapeutic monitoring).
- FDA-cleared: GE (2009), Siemens (2012), Philips (2014).
- Available on both – 1.5T and 3T platforms.
- Acquisition time: ~ 1 minute GRE based; 15 seconds SE-EPI based
- Installed clinical base: > 900 systems worldwide.



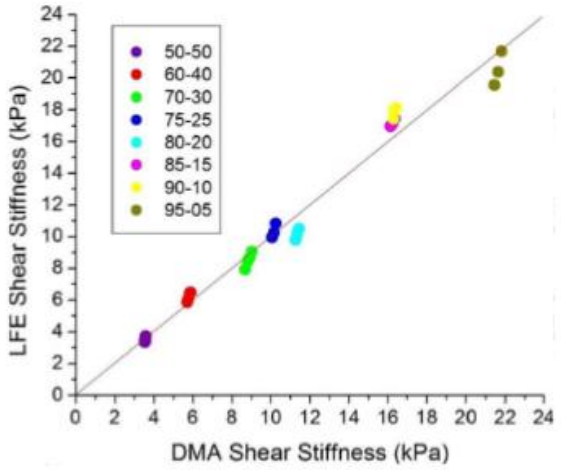
Measurement Accuracy of MRE

Average ± Standard Deviation of Shear Modulus (kPa)
Calculated from Dynamic Mechanical Analysis and MRE



%Agar	DMA	MRE manual
1.5	14.28 ± 1.34	17.42 ± 1.12
2	25.02 ± 0.21	33.54 ± 1.56
2.5	49.26 ± 1.38	52.28 ± 2.28
3	80.81 ± 1.57	86.07 ± 4.02
3.5	108.30 ± 4.35	108.10 ± 8.89

Ringleb et al. MRM (2005)



Plot of DMA vs MRE shear stiffness. The dotted line is the line of unity. ICC = 0.99 (95% CI = 0.97-0.99)

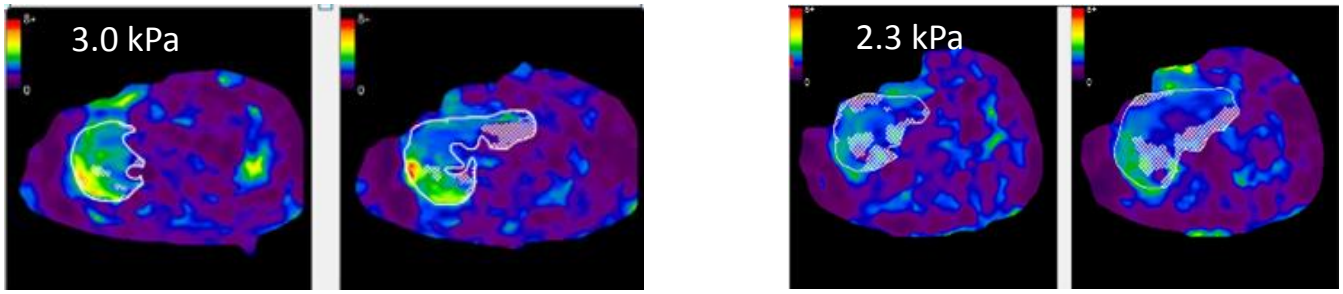
Arunachalam et al. MRM (2016)

Purpose of this study: MRE Profile Longitudinal Claim Test – Retest Repeatability

For a given measured percentage change in the magnitude of the complex shear modulus, a plausible range for the true change is the measured change, with 95% confidence.

(Assuming no change in hardware and software platform and analysis method.)

Pre-Treatment → (6 months) → Post-Treatment



Example: 15 year old patient with NASH

Methods: MRE repeatability search

Library 1: 309 articles found through database search.

Library 2: 350 articles found through database search.

Duplicate articles removed and list combined in single endnote. 450 articles collected.

Articles were independently screened by two observers for repeatability and reproducibility studies.

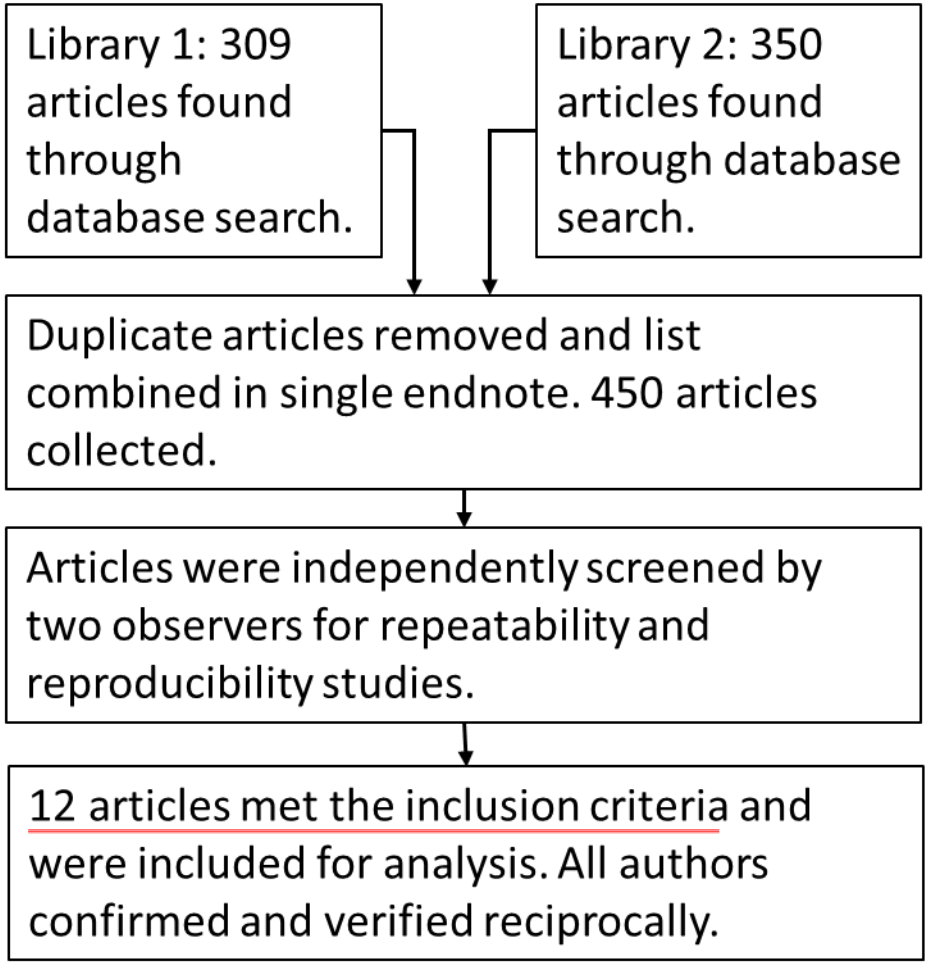
Inclusion criteria:

1. studies that reported measurements of change in liver stiffness measured at two of more timepoints under similar conditions;
2. studies that reported MRE-based stiffness values as absolute value of shear modulus;
3. studies that reported the time between repeat measurements, mean liver stiffness and the coefficient of variation.

Exclusion criteria:

1. duplicate publication (based on the same primary study);
2. non-original research; and
3. studies not published in English.

Methods: MRE repeatability search



From the 12 studies, the following data were extracted:

(1) Author, journal and year of publication;
(2) number of subjects;
(3) number of readers;
(4) within-subject Coefficient of variation (wCV);
(5) notes on method used to calculate the wCV.

Results: 12 studies comprising of 274 patients met the inclusion and exclusion criteria.
Publication range: 2010 – 2016.

	Study	Year	Study design	Sample size	Age range	Male %	MR scanner	Field strength	Frequency (Hz)	Property measured	Subjects	No. of readers	Time interval	COV reported(%)	fasting vs feeding
1	Wang et Al	2011	Prospective	5	NA	NA	Siemens Espree	1.5 T	60	Magnitude	Healthy subjects	2	2 weeks	9 - 12%	No information
2	Venkatesh et Al	2014	Prospective	41	23 - 63	44	GE HDx	1.5 T	60	Magnitude	Healthy subjects	2	4 - 6 weeks	8.4	4 - 6 hrs. fasting
3	Shire et Al	2011	Prospective	9	20 - 57	44	GE HDx	1.5 T	60	Magnitude	5 healthy, 4 patients	3	1 - 2 weeks	6 - 11%	8 hrs. fasting
4	Shinagawa et Al	2014	Prospective	10	27 - 63	90	GE 750W	3.0 T	60	Magnitude	Healthy subjects	1	1 week	NA	No information
5	Shin et Al	2014	Retrospective	15	57 (mean)	NA	GE HDx	1.5 T	60	Magnitude	patients	2	2 weeks	NA	No information
6	Shi et al	2014	Prospective	22	18 - 56	41	GD HD	3.0 T	60	Magnitude	Healthy subjects	2	1 week - short term; 27 - 30 wks - long term	5.75	8 hrs fasting
7	Lee YJ et Al	2014	Retrospective	47	27 - 82	68	GE HDx	1.5 T	60	Magnitude	patients	2	8 - 10 mins.	13	No information
8	Jajamovich et al	2014	Prospective	30	55.8 (mean)	77	GE 750	3.0 T	60	Magnitude	11 healthy, 19 patients	2	20 minutes	3.8	6 hrs fasting and then repeated after feeding
9	Hines et al	2010	Prospective	30	21 - 68	53	GE HDx	1.5 T	60	Magnitude	20 volunteers, 10 patients	2	2 - 4 weeks	17.4	No information
10	Hines et al	2011	Prospective	11	23 - 39	75	GE HDx	1.5 T	60	Magnitude	Healthy subjects	1	5 weeks	8.5	feeded between scans
11	Bohte et al	2013	Prospective	30	19 - 59	60	Philips	3.0 T	50	Magnitude, Propogation velocity	16 volunteers, 14 patients	1	1 - 4 weeks	10.1	No information
12	Trout et al	2016	Prospective	24	22 - 55	21	GE & Philips	1.5T & 3.0T	60	Magnitude	Healthy subjects	1	same day	10.7	6 - 8 hrs. fasting

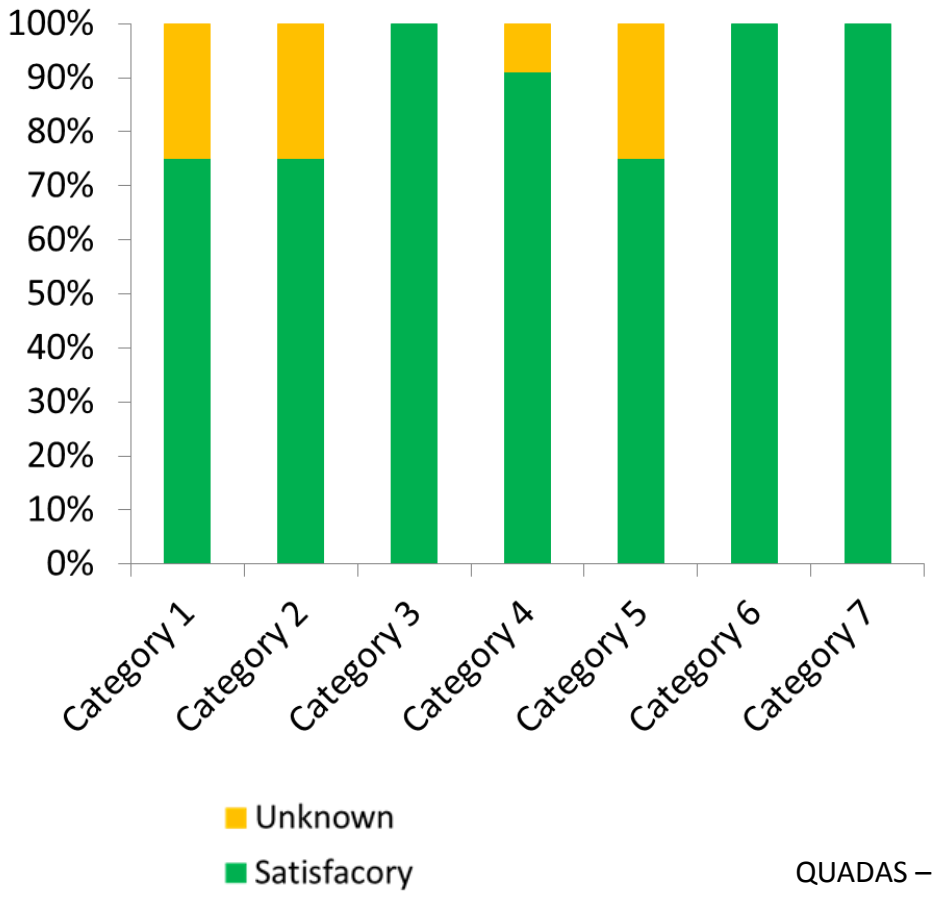
Table – Baseline characteristics of included studies.

QUADAS-2 tool

Ann Intern Med. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009.

QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.

Whiting PF[1], Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group.



Risk of Bias

1. Patient Selection
2. Index Test
3. Reference Standard
4. Flow and Timing

Applicability Concerns

5. Patient Selection
6. Index Test
7. Reference Standard

QUADAS – Quality Assessment tool for Diagnostic Accuracy Studies.

Statistical Analysis

(courtesy: Nancy Obuchowski, Ph.D.)

Repeatability Coefficient was calculated:

$$\%RC = 1.96 \times \sqrt{2 \times \%wCV^2}$$

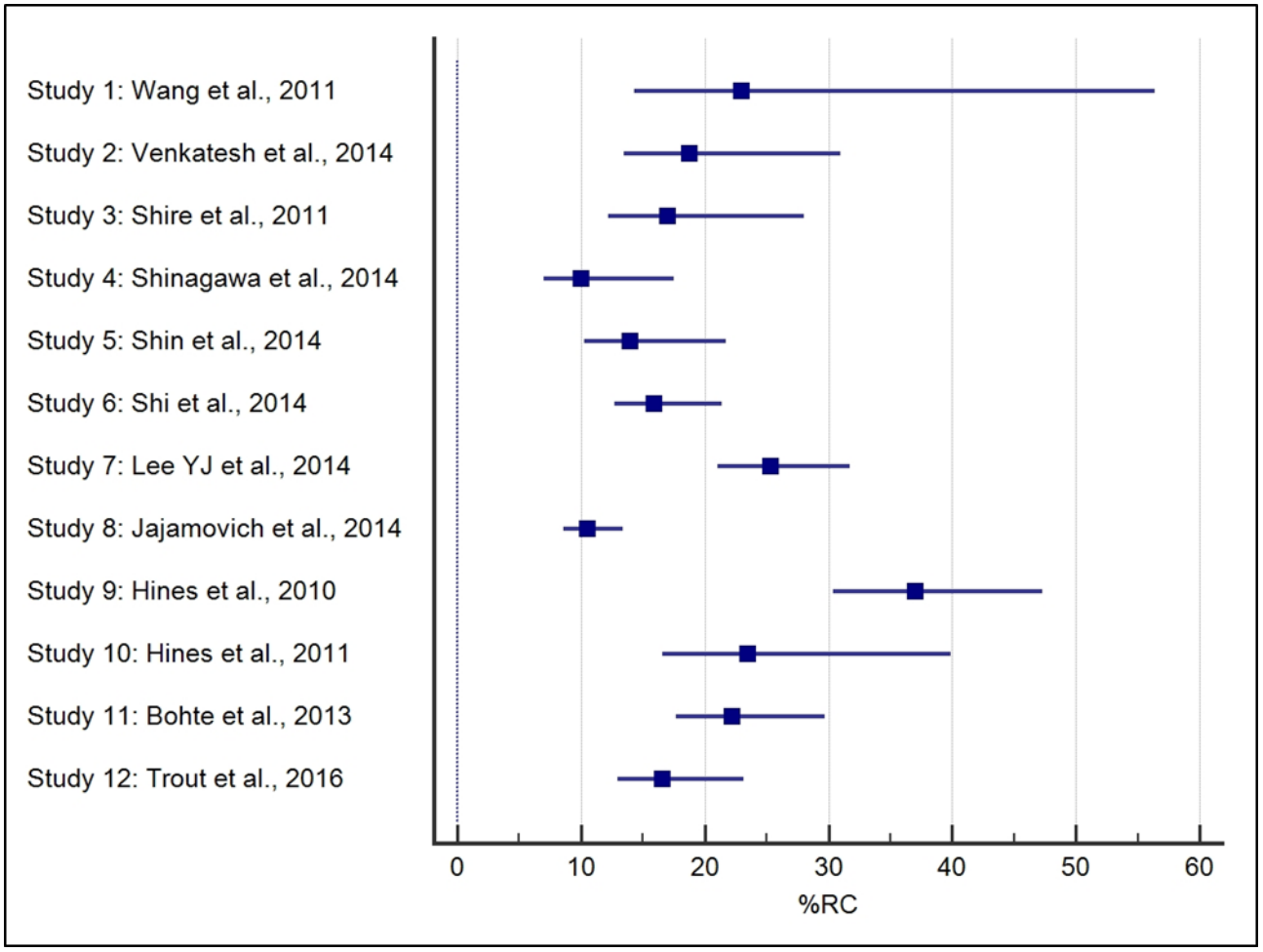
where %wCV is the within-subject coefficient of variation.

The 95% confidence interval (CI) for the RC for each study was calculated as:

$$2.77 \times \sqrt{M \times \%wCV^2 / \chi^2_{M,\alpha}}$$

where $\chi^2_{M,\alpha}$ is the αth percentile of the chi square distribution with M degrees of freedom. For the lower bound, α is 0.975, and for the upper bound, α is 0.025.

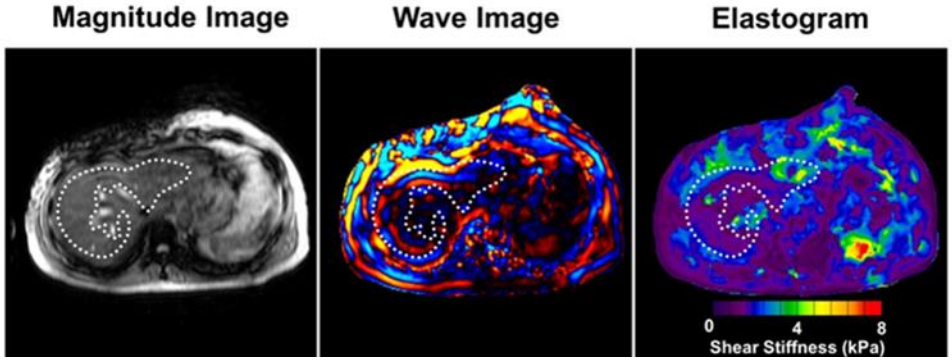
Results



Forest Plot from 12 studies: Summary **RC = 22%** [16.1 – 28.2]

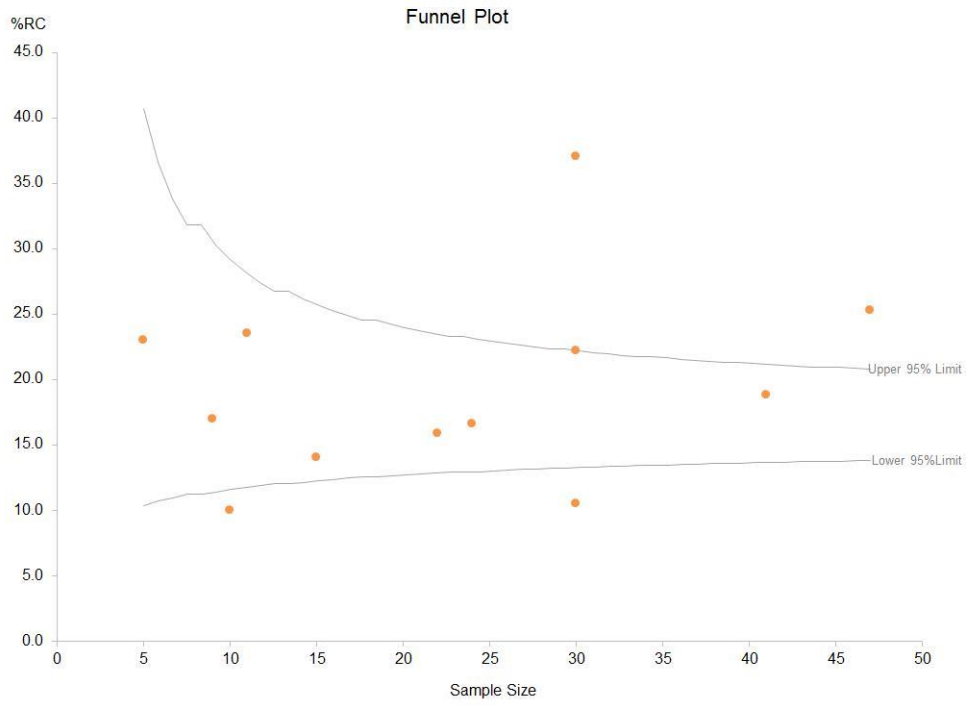
Results

	# studies	Summary RC	95% bootstrap CI
Trained operator to draw ROI	10	18.4	[14.2, 22.2]
≤1 week between scans	5	17.5	[11.6, 23.4]
> 1 week between scans	5	19.3	[15.6, 21.8]
Untrained operator to draw ROI	2	34.5	--
1.5 field strength	8	25.2	[17.4, 31.9]
≤1 week between scans	2	21.7	--
> 1 week between scans	6	26.0	[16.7, 34.2]
3.0 field strength	4	15.6	[10.5, 20.8]
≤1 week between scans	3	12.7	[10.0, 15.9]
> 1 week between scans	1	22.2	--
All 12 studies	12	22.0	[16.1, 28.2]



Results

Funnel Plot was generated to address publication bais.



Funnel plot of the RC estimates from each study (on the y-axis) versus the effective sample size (on the x-axis). The funnel plot shows that studies with the large sample size fall near the summary value of 22%, and smaller studies fall fairly symmetrically on either side towards the bottom of the plot.

Conclusion

- MRE is a repeatable, non-invasive method for detecting and staging liver fibrosis.
- Our estimated meta-analysis summary: Repeatability coefficient: 22% with a 95% CI of [16.1 – 28.2]
- Assuming no change in MRE hardware and software, a change of 22% or larger can be considered a true change.

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- Richard L. Ehman, MD, PhD (Co-Chair)
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