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Low field, open bore MRI proton density fat fraction for steatosis and nonalcoholic steatohepatitis diagnosis: a study in a population of 150 morbidly obese bariatric surgery candidates

P. Garteiser[1], M. Esposito Farese[2], S. Doblas[1], F. Dib[2], M. Dioguardi Burgio[3], V. Vilgrain[3], M. Coupaye[4], P. Jouet[4], B. Van Beers[1,3]

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Low field MRI of liver disease in morbid obesity

BACKGROUND

Background

25 — 29.9 — 35 — 40 → body mass index (kg/m²)

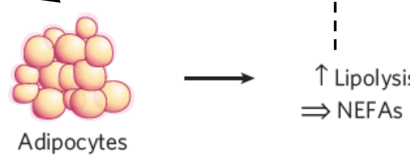
overweight | obesity | severe obesity | morbid obesity

type 2 diabetes

85-95%

NAFLD

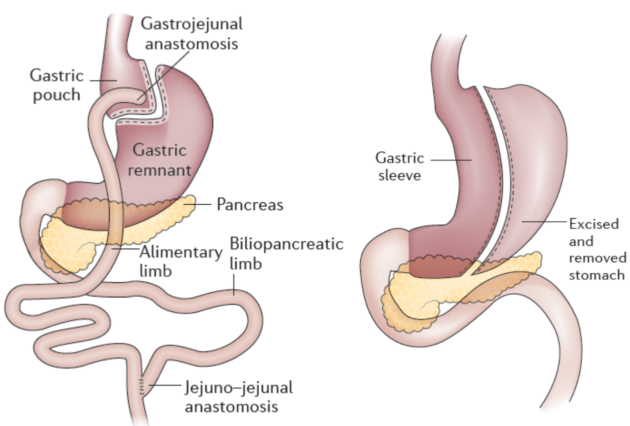
- steatosis (91%)
- steatosis + inflammation = NASH (37%)



fibrosis (60%)

cirrhosis

cancer



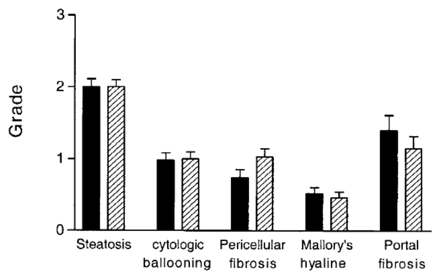
Nguyen, Nat Rev Gastroent & hepatol

bariatric surgery: improves T2D, NAFLD and hypertension

Background

- Role of NAFLD in obesity pathophysiology?
- Assessment of liver status in morbidly obese population
  - Clinical tests: indirect, weak diagnostic performance
  - Blood tests: indirect, weak diagnostic performance

Normal ALT (■)
Elevated ALT (▨)



Mofrad & al. Hepatol 2003

  - Biopsy: gold standard, but sampling variability, risk and difficult in MO patients
- Need of an imaging tool for liver status diagnosis
- "FIRM" cohort (Mourier & Beaujon Hospitals)

Background

- MR of morbid obesity
- Spectroscopy studies of morbid obesity
  - Limited number of patients (NASH n=1 in *van Werven & al. Hepatic steatosis in morbidly obese patients undergoing gastric bypass surgery: assessment with open-system 1H-MR spectroscopy. AJR Am J Roentgenol. 2011;196(6):W736-42*)
  - Gold standard not always available *Springer & al. Quantitative assessment of intrahepatic lipids using fat-selective imaging with spectral-spatial excitation and in-/opposed-phase gradient echo imaging techniques within a study population of extremely obese patients: feasibility on a short, wide-bore MR scanner. Invest Radiol. 2010;45(8):484-90.*
- MR imaging studies of morbid obesity
  - Dual echo sequences do not provide R2* compensation or quantification *Hedderich & al. Effects of Bariatric Surgery on Non-alcoholic Fatty Liver Disease: Magnetic Resonance Imaging Is an Effective, Non-invasive Method to Evaluate Changes in the Liver Fat Fraction. Obes Surg. 2017;27(7):1755-62*
- Multiple echo gradient echo sequences hold promise for accurate fat and R2* quantification
  - *Leporq B, Lambert SA, Ronot M, Vilgrain V, Van Beers BE. Simultaneous MR quantification of hepatic fat content, fatty acid composition, transverse relaxation time and magnetic susceptibility for the diagnosis of non-alcoholic steatohepatitis. NMR Biomed. 2017;30(10).*

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METHODS

Patients & Methods

Patients

- Enrollment:
  - Morbid obesity (IMC > 35 kg/m^2)
  - Prescription of bariatric surgery
  - Perisurgical biopsy
  - Age > 18, informed consent
  - Monocentric (Louis Mourier Radiology dept.)

- Exclusion:
  - > 230kg
  - Anteropost diameter > 40cm
  - Alcohol consumption (>20,30g/day for women, men, resp.)
  - Pregnancy
  - Known hepatopathy (HIV, HCV, hemochromatosis)

Patients & Methods

"FIRM" Protocol

- MRI
  - Proton density fat fraction
  - Diffusion weighted imaging (IVIM b values sampling)
- US transient elastometry
  - "Liver stiffness"
  - Controlled attenuation parameter
- Clinical tests
  - Steatotest
  - NASHtest
  - Actitest
- Biopsy analysis
  - Steatosis (degree and morphometry)
  - Absence / presence of NASH

Steatosis at histology	
Number of lipid-positive hepatocytes	degree
<5%	0
5-33%	1
33-66%	2
>66%	3 "severe"

Patients & Methods

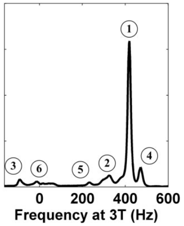
MRI sequence

- 1.0T/42MHz open-bore MRI (vertical field), butterfly coils
- Gradient echo sequence with multiple echoes
- 14 echoes from 3.46ms to 48.3ms (interecho spacing at 42MHz: 3.46ms). FA=10°.
  - First echo on the first available OP time
  - Interecho spacing equal to IP-OP spacing for "optimal" sampling
- Geometry:
  - FOV: 41x45cm (1.875mm in-plane resolution)
  - 3 slices, 1cm slice thickness
- Single 17,6s breath hold

Patients & Methods

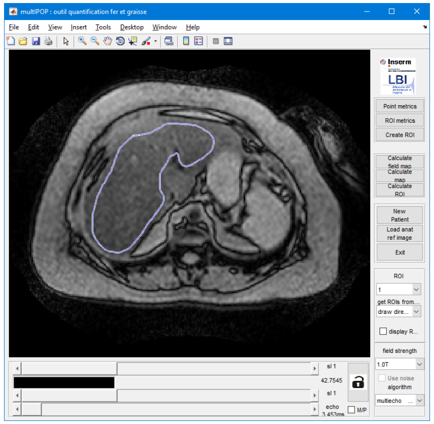
Fat fraction calculation - 2

- Fitting procedure
  - Degrees of freedom: S_0, PDFF, water T2*, fat T2*
  - Spectral modelling; water peak + 6 most abundant fat species (21 intereferences) *(Yu, MRM 2008)*

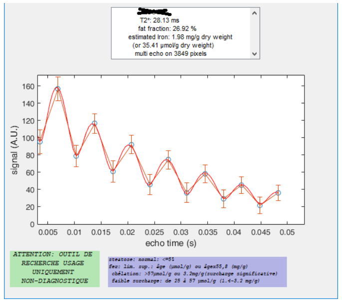



```
%magn only, 6-peaks fat spectrum, two T2* compartments
w     = [  0.047    0.039    0.006    0.12    0.70    0.0880];
OMEGf = 2*pi().* (B0/3) .* [-76.8 64 249.6 332.8 435.2 486.4] .* t;
OMEGw = 2*pi() * (B0/3) * 0 * t;
f = sqrt( ((SIwat^2)*exp(-2*t/T2wat)) +(w(1)^2+w(2)^2+w(3)^2+w(4)^2+w(5)^2+w(6)^2)*((SIfat^2)*exp(-2*t/T2fat)) + ...
    2*((SIfat^2)*exp(-2*t/T2fat)) *( ...
    w(1)*w(2)*cos(OMEGf(2)-OMEGf(1))+w(1)*w(3)*cos(OMEGf(3)-OMEGf(1))+w(1)*w(4)*cos(OMEGf(4)-OMEGf(1))+w(1)*w(5)*cos(OMEGf(5)-OMEGf(1))+w(1)*w(6)*cos(OMEGf(6)-OMEGf(1))+ ...
                                      w(2)*w(3)*cos(OMEGf(3)-OMEGf(2))+w(2)*w(4)*cos(OMEGf(4)-OMEGf(2))+w(2)*w(5)*cos(OMEGf(5)-OMEGf(2))+w(2)*w(6)*cos(OMEGf(6)-OMEGf(2))+ ...
                                                                        w(3)*w(4)*cos(OMEGf(4)-OMEGf(3))+w(3)*w(5)*cos(OMEGf(5)-OMEGf(3))+w(3)*w(6)*cos(OMEGf(6)-OMEGf(3))+ ...
                                                                                                         +w(4)*w(5)*cos(OMEGf(5)-OMEGf(4))+w(4)*w(6)*cos(OMEGf(6)-OMEGf(4))+ ...
                                                                                                                                           +w(5)*w(6)*cos(OMEGf(6)-OMEGf(5))) + ...

    2*((SIfat)*exp(-t/T2fat))*((SIwat)*exp(-t/T2wat))*( ...
                  w(1)*cos(OMEGw-OMEGf(1))+ ...
                  w(2)*cos(OMEGw-OMEGf(2))+ ...
                  w(3)*cos(OMEGw-OMEGf(3))+ ...
                  w(4)*cos(OMEGw-OMEGf(4))+ ...
                  w(5)*cos(OMEGw-OMEGf(5))+ ...
                  w(6)*cos(OMEGw-OMEGf(6))));
```



  - Echo-wise SNR regularization
  - Initialization:
    - PDFF: 3 points Dixon
    - S_0: extrapolation to TE=0;
    - T2*: linear approximation on 3 first in phase echoes



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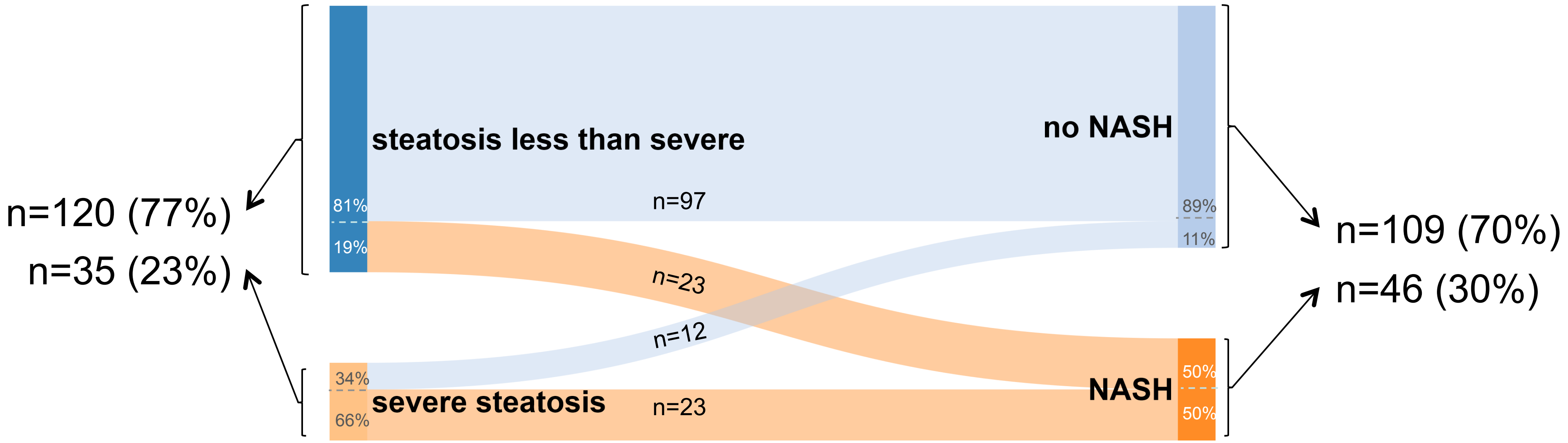
RESULTS

Results

Cohort statistics

n	= 186
n(MRI)	= 155, all biopsied
Inclusion duration:	36 months of inclusion
Age:	18-64 years
Body mass:	80-168 kg (median: 121kg)
Height:	148-186 cm
BMI:	35-63 kg/m² (median: 43kg/m²)
Known diabetes:	38 of 186 patients (21%)

NASH vs. histologically severe steatosis:

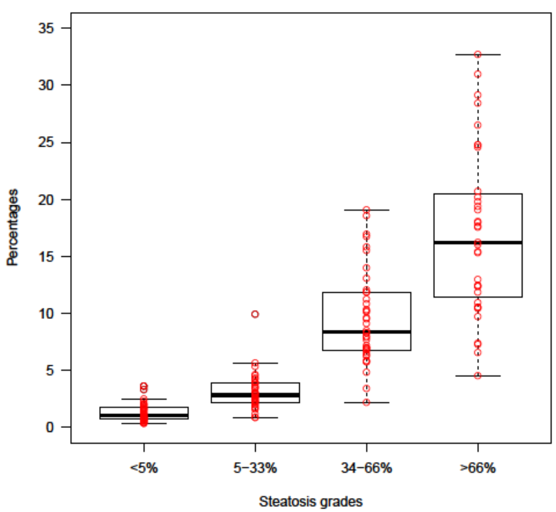


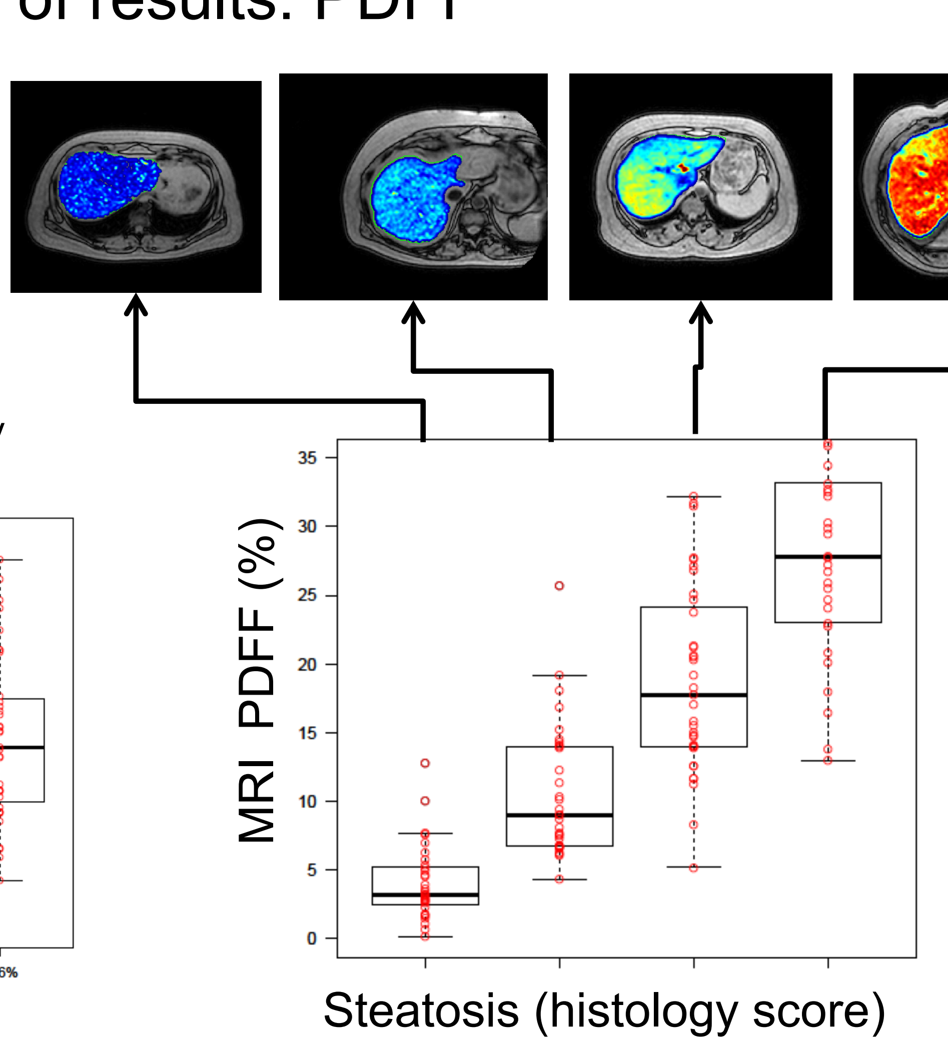
Results

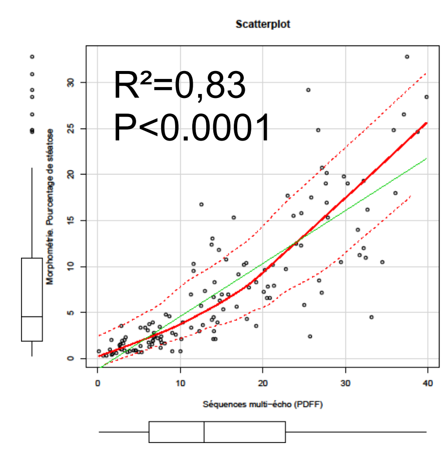
PDFF to score steatosis

- Distribution of results: PDFF

Steatosis morphometry vs. grading



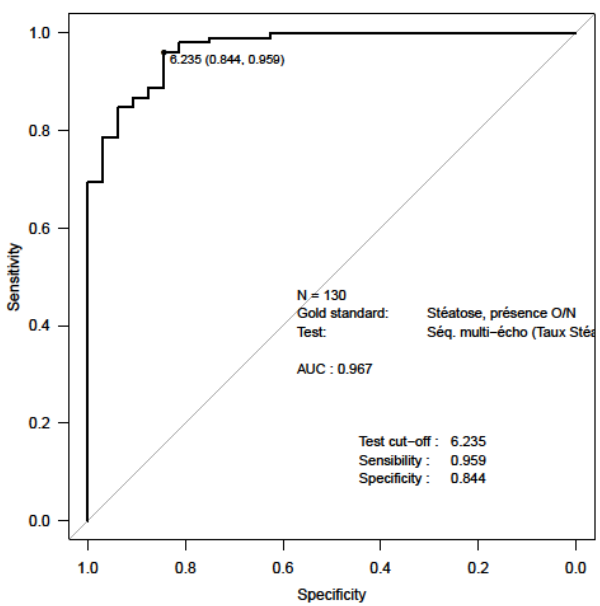




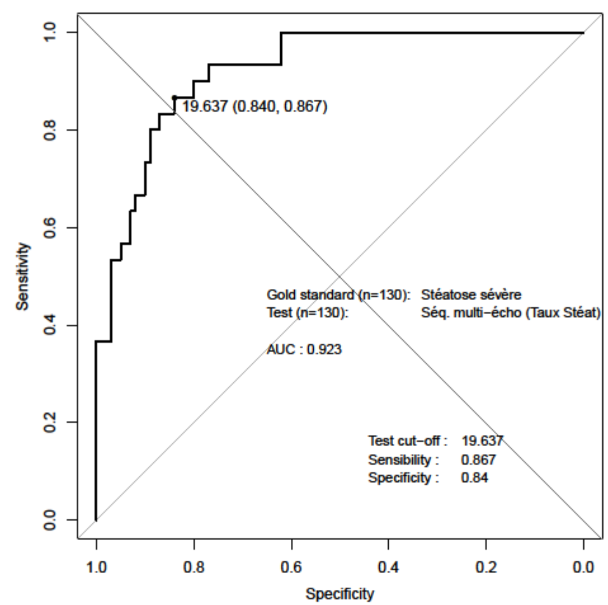
Results

PDFF AuROC for steatosis

- Presence of steatosis AUC (n=42 vs. n=113):
  - MRI: 0.97 (Se/Sp 96/84% @ 6.2%$_{v/v}$)
  - Steatotest: 0.75 (Se/Sp 73/67% @ 0.54)
  - Fibroscan CAP: 0.84 (Se/Sp 80/85% @ 314)

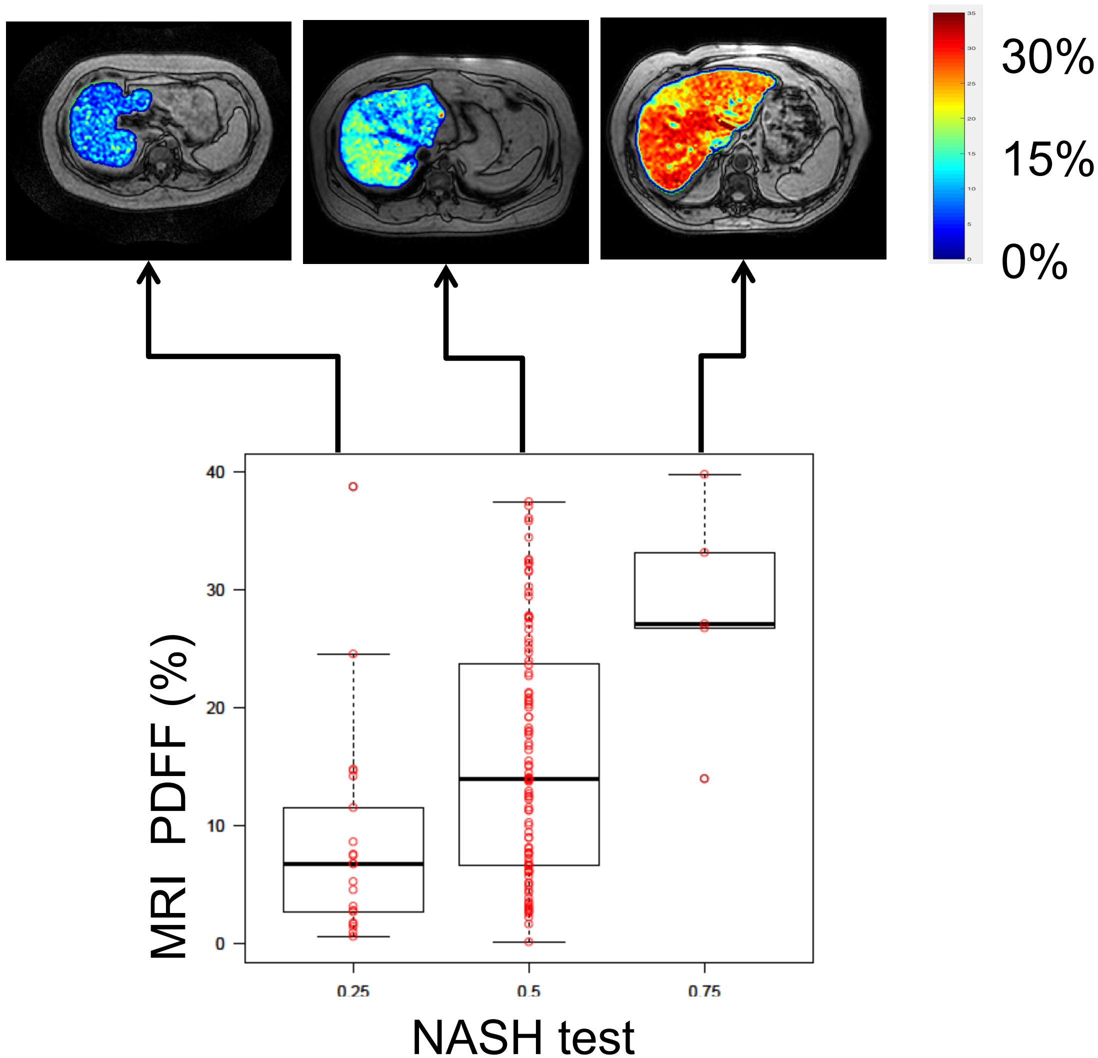


Severe steatosis AUC (n=120 vs. n=35):
- MRI: 0.92 (Se/Sp 87/84% @ 19.6%$_{v/v}$)
- Steatotest: 0.80 (Se/Sp 74/71% @ 0.65)
- Fibroscan CAP: 0.74 (Se/Sp 84/66% @ 342)



Results

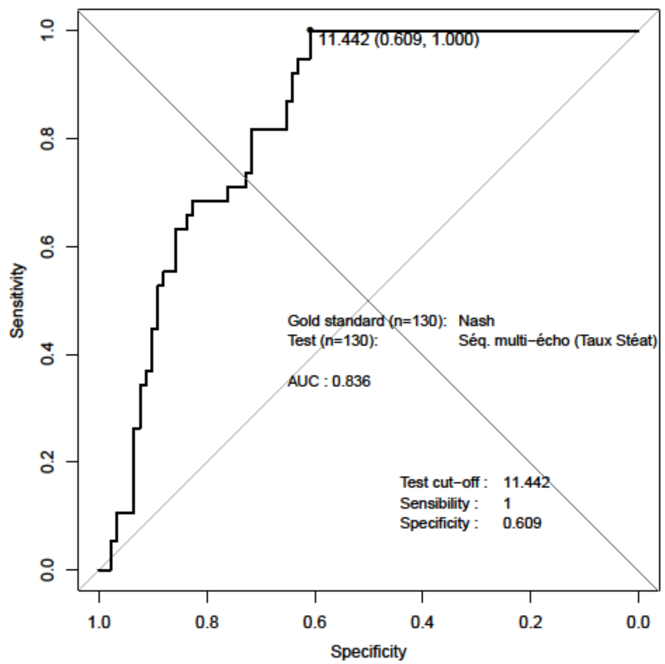
PDFF to detect NASH



Results

PDFF to detect NASH

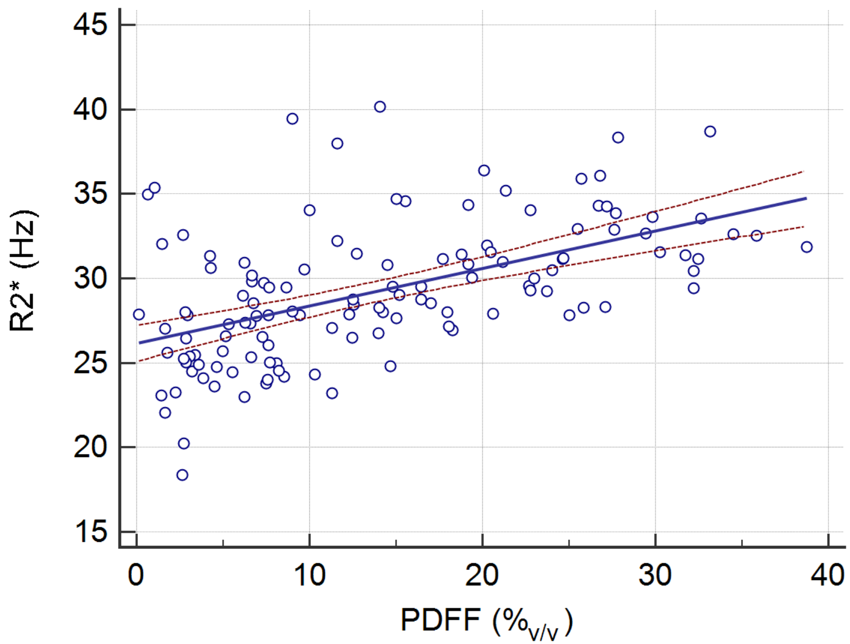
presence of NASH:
AUC PDFF: 0.84 (Se/Sp 100/61% @ 11%$_{v/v}$)
Actitest: 0.75 (Se/Sp 89/50% @ 0.08)
Fibroscan stiffness: 0.67 (Se/Sp 58/73 @ 7.6kPa)
Fibroscan CAP: 0.69 (Se/Sp 97/38% @ 291)



Results

Other MRI markers

- R2*: significant association to PDFF
  - similar responses than PDFF, but with lower diagnostic accuracy
  - High PDFF correlated with higher R2* (r=0.54, p<0.0001)
    - Cross talk in the fit ?
    - Involvement of inflammation ?
    - Iron deposition ?



Low field MRI of liver disease in morbid obesity

CONCLUSION

Conclusions

- Feasibility of measuring PDFF at 1.0T
- PDFF measurement by low-field MRI is an accurate estimation of biopsy histological score of NASH and steatosis
- PDFF performance is significantly better than blood tests and fibroscan for steatosis and inflammation (gold standard: histology analysis of biopsy)
- Next steps:
  - Study of organ heterogeneity; radiomics analysis
  - Involvement of fibrosis: MR elastography ("Quid-NASH" RHU cohort n = 2×350, diabetes recruitment)
  - Improvements in the fit procedure (accuracy, robustness)

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Thank you

Muriel Coupaye
Danielle Calabrese
Séverine Ledoux
Pierre Bedossa
Laurent Castera

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THANK YOU FOR YOUR ATTENTION

Low field, open bore MRI proton density fat fraction for steatosis and nonalcoholic steatohepatitis diagnosis:
a study in a population of 150
morbidly obese bariatric surgery candidates

Philippe Garteiser

université PARIS DIDEROT PARIS 7

LBI *Laboratoire des Biomarqueurs en Imagerie*

Thanks:
Feryel Mouri
Pr. Marcellin
Louis Mourier Hospital

HÔPITAL BEAUJON

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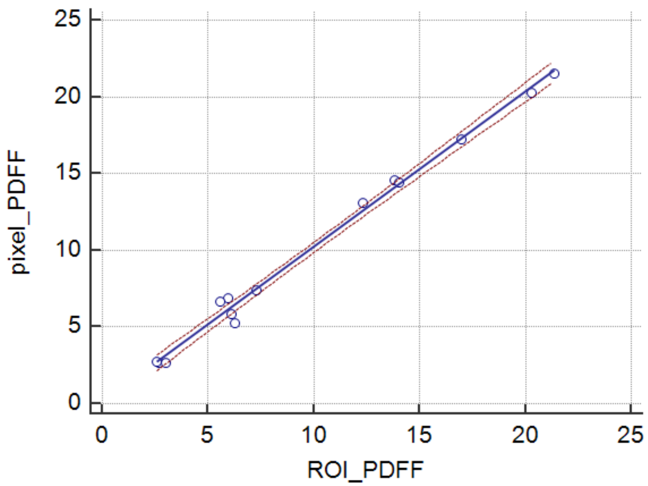
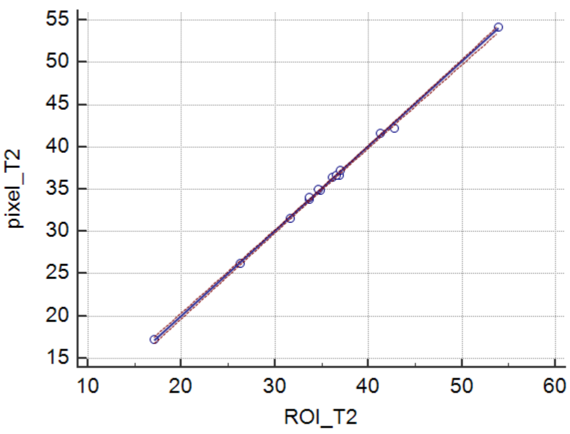
- Pixewise vs. roiwise

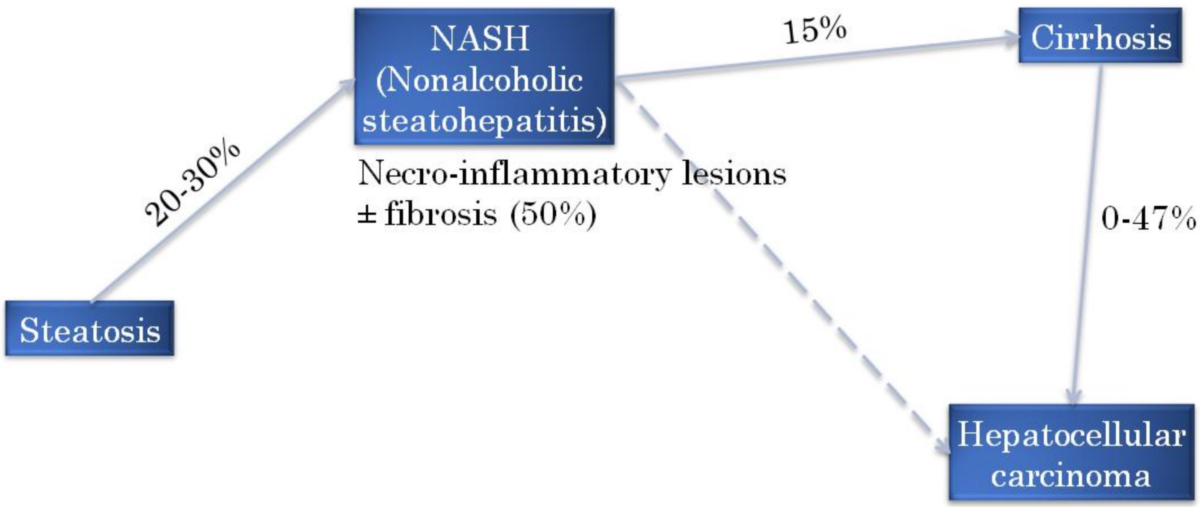




Background

- Severe obesity: BMI > 35kg/m²
- Obesity: increasing prevalence
- NAFLD: spectrum of disease

  Steatosis -> nonalcoholic steatohepatitis -> cirrhosis -> liver failure



According to: Tiniakos 2010 Ann. Rev. Pathol.

- NAFLD development: driven by obesity and insulin resistance

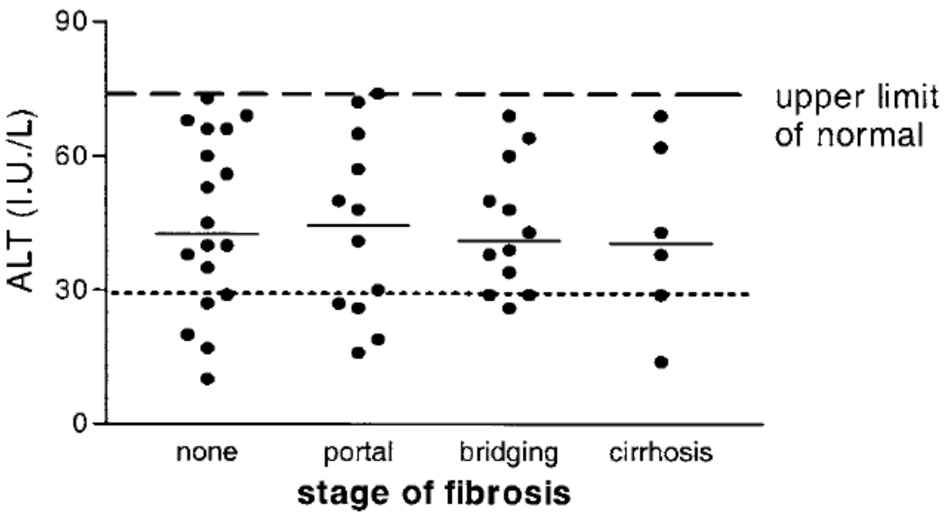
Walle 2016

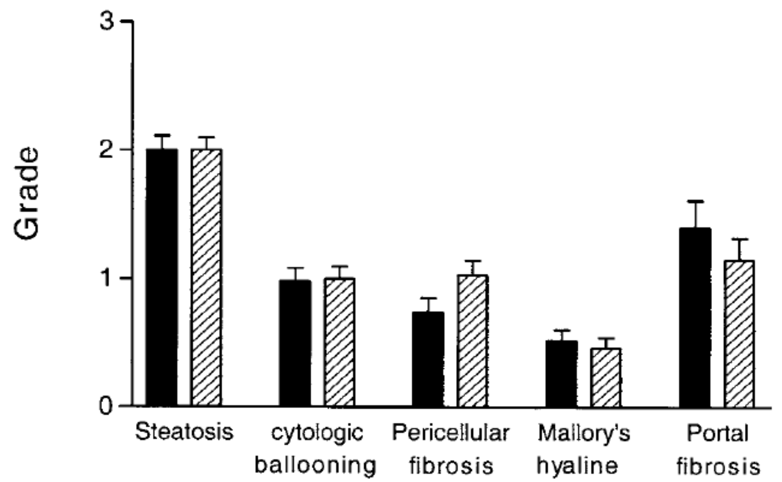
- NASH = steatosis + inflammation and cytological ballooning
- NASH: increased risk for end stage liver disease and cardiovacular disease
- Insulin resistance: induces lipolysis in adipose tissue, releasing free fatty acids
- Free fatty acid = major source of triglycerides for liver storage !
- Hence looking @ liver steatosis as status of adipose metabolism ?

Background

Diagnostic methods

- Biopsy: limited sampling size, associated risk, high cost
- Serum aminotransferases
  - The entire NAFLD spectrum can be seen in patients with normal serum levels ! (Mofrad, Hepatol. 2003)





51 subjects with NAFLD and normal ALT (■)

50 subjects with NAFLD and elevated ALT levels (▨)

Background

Morbid obesity

- Threshold: BMI ≥ 40kg/m²
- Patient corpulence sometimes incompatible with conventional MRI systems
- Open-field designs: vertical field; patients up to 250kg
- Limits: lower field strength (1.0T)
- 1.0T, open-field design: applicable for MRS determination of fat *(Chabanova, Abd. Imag. 38(2), 2013)*
- Feasibility of assessing PDFF by imaging at 1.0T ?