NCSCG
AASLD 2016 Review

Fatty Liver Disease

ID: 1056. Burden of Nonalcoholic Fatty Liver Disease (NAFLD) in the United States.

- Background:
  - NAFLD and its impact on health care resource utilization needs to be defined.
- Aim: To develop a comprehensive model of the burden of disease and its financial impact through 2030.
- Methods:
  - The prevalence of NAFLD and its histological subtypes (NAFL and NASH) were computed from national data on trends for obesity and T2DM separately. and then applying the prevalence rates of NAFL and NASH from published literature to these data.
  - The two data sets were integrated to develop a comprehensive model of NAFLD in the US population.
  - Transition rates towards cirrhosis, end stage liver disease and cancer corrected were computed from a comprehensive literature search.
  - Competing mortality from other background causes were estimated to assess the impact of NAFLD on excess all cause, liver-related and cardiovascular deaths.
  - Model results were validated based upon national surveillance data for annual HCC incidence attributable to NASH.

Figure 1. NAFLD Disease Progression Model

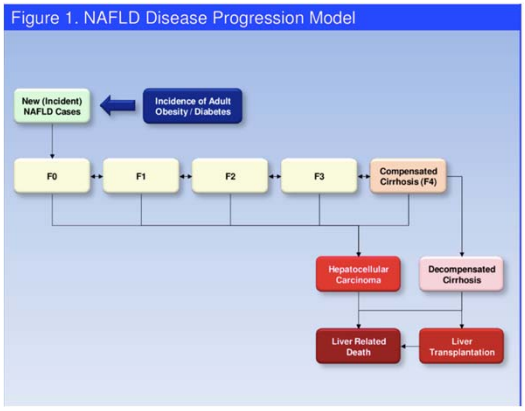
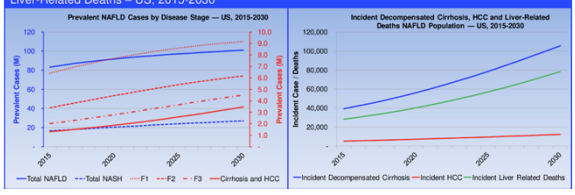
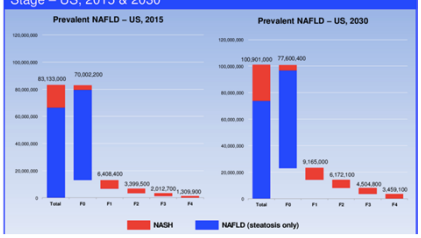


Figure 2. Prevalent NAFLD Cases by Disease Stage and Incident Decompensated Cirrhosis, HCC and Liver-Related Deaths – US, 2015-2030



- NAFLD cases will increase from 83 million in 2015 to 101 million in 2030, a 20% increase.
- Total NASH cases will increase from 16.5 million in 2015 to 27.0 million in 2030, a 65% increase.
- The number of incident NASH-related HCC cases is projected at 12 220 in 2030, an increase of nearly 140% as compared to 2015 (5150 cases).
- The prevalent number of compensated and decompensated cirrhosis cases are projected to increase 180% and 200% from 2015 to 2030 (3 046 200 and 375 600 cases in 2030), respectively.

Figure 3. Distribution of Prevalent NAFLD Population by Fibrosis Stage – US, 2015 & 2030



Projected direct healthcare costs for NAFLD-related end stage liver disease will increase 165% from 9 570 M to 25 380 M USD during 2015-2030. By 2030, liver related mortality is estimated at 78 200 deaths, an increase of 200% from 2015 (26 280 deaths).

Conclusions: With the projected increase in T2DM and a flattening of obesity prevalence, there will be a disproportionate increase in NASH over the next 15 years.
This will translate in to a substantial increase in the burden of cirrhosis, end stage liver disease and HCC resulting in a commensurate increase in health care costs.

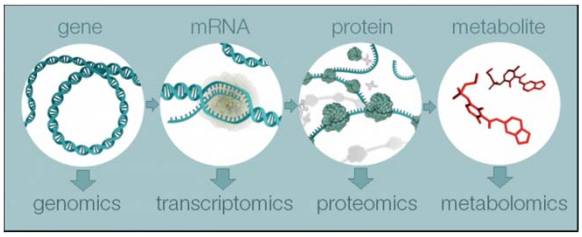
31: No Benefit from Modest Alcohol Use in NAFLD

- Background: Cross sectional studies report a lower prevalence of severe disease in modest drinkers compared to abstinent
- Aim: Evaluate the longitudinal association between modest alcohol use and changes in histologic features of NAFLD in paired biopsies
- Methods : NASH CRN participants
  - > 2 drinks/day excluded,
  - former drinkers excluded.
  - Difference in NAS evaluated by ANCOVA
- Results: 304 patients
  - 83% white,
  - 70% female,
  - mean age 47.
  - 187 (63 %) modest alcohol use vs. 117 abstinent.

Changes in Histologic Features from Baseline to Follow up Biopsy

	Drinking status				
	Non-drinker (N=117)		Modest drinker (N=187)		
Histologic feature (Change)	Mean ± SD	Adjusted mean	Mean ± SD	Adjusted mean	P*
Steatosis	**-0.43 ± 0.9**	**-0.48**	**-0.32 ± 0.9**	**-0.29**	**0.03**
Ballooning	-0.31 ± 1.0	-0.25	-0.13 ± 0.9	-0.17	0.42
Lobular inflammation	-0.22 ± 0.9	-0.26	-0.28 ± 0.9	-0.26	0.99
Overall NAS	-0.96 ± 2.1	-0.99	-0.73 ± 2.0	-0.71	0.16
Portal inflammation	+0.16 ± 0.7	+0.18	+0.11 ± 0.7	+0.10	0.27
Fibrosis	+0.03 ± 1.2	+0.05	+0.11 ± 1.0	+0.10	0.65

Conclusion: Modest alcohol use is associated with less improvement in steatosis on paired biopsies and no statistical difference in other other histological features including fibrosis. Conflicts with findings from cross-sectional studies.



http://www.ebi.ac.uk/training/online/sites/ebi.ac.uk.training.online/files/user/2760/images/Metabolomics/central_dogma_figure_1_.png

40:Metabolomics in a liquid biopsy provides a noninvasive comprehensive NAFLD-diagnostic tool.

- Background: Need for point of care diagnostic tool for NASH
- Hypothesis: Metabolic changes reflected on circulating metabolome
- Aims: Use serum/plasma metabolomic to create a model to
  - Differentiate NAFLD from controls
  - Assess severity of steatosis
  - Distinguish between NAFL and NASH
  - Identify presence of any or advanced fibrosis
- Methods
  - 652 patients used to develop model
  - 295 patients in validation cohort
- Results
  - 817 NAFLD patients
  - 130 control

Results

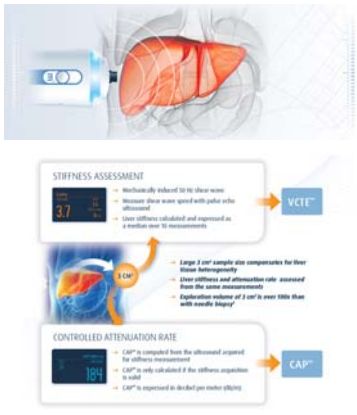
Fibrosis assessment: 185 NAFLD patients , F0=71, F1&F2=80, F3&F4=34
MODEL F1&F2 vs. F3&F4 AUC 0.89±0.03

	NAFLD *vs.* Control (OWLiver Care)					
	Total	Control	NAFLD	AUC	PPV	NPV
Test (N)	467	90	377	0.90±0.02	0.89	0.88
Validation (N)	295	40	255	0.93±0.03	0.97	0.79
	NAFL *vs.* NASH (OWLiver)					
	Total	NAFL	NASH	AUC	PPV	NPV
Test (N)	377	246	131	0.95±0.01	0.89	0.90
Validation (N)	255	108	147	0.84±0.03	0.93	0.76

Conclusion: Proof of concept of liquid biopsy metabolomics in diagnosis of NASH

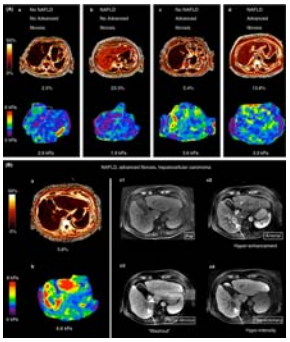
42:Prospective Comparison to Liver Biopsy of VCTE/CAP, MRE,PDFF and Multiparametric MRI for Predicting Degree of Steatosis and Diagnosis of NASH.

- Background: NAFLD diagnosis limited to histopathology. Newer imaging modalities available.
- Aims: Assess the ability of these techniques to predict steatosis and assess disease severity.
- Methods: Prospective enrollment
- Results

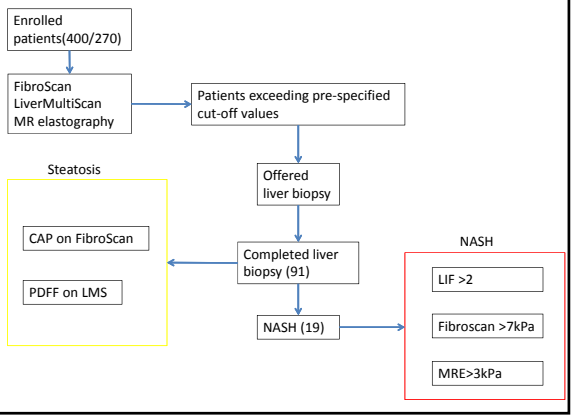


http://www.echosens.us/technology

Proton Density Fat Fraction



Sep 2015 · Alimentary Pharmacology & Therapeutics



Steatosis Grade	0	1	2	3
PDFF(%)	4.38	8.64	17.04	23.17
CAP(dB/m)	276.8	313.8	358.8	350.3

P<0.05 by Kruskal-Wallis

Imaging Modality Table

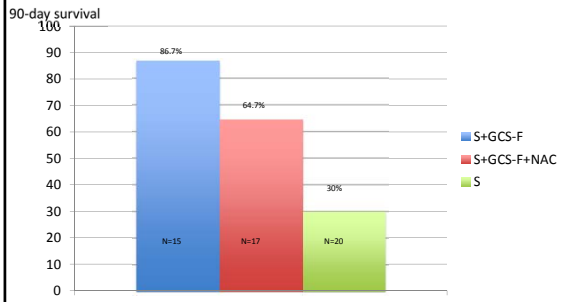
Imaging Modality	Sensitivity	Specificity	PPV	NPV
LIF score > 2	0.93	0.32	0.25	0.95
Fibroscan > 7 kPa	0.69	0.80	0.48	0.91
MRE > 3 kPa	0.33	0.98	0.83	0.85

Conclusion:
CAP and PDFF are valid methods for predicting grade of hepatic steatosis.
LIF<2, Fibroscan <7kPa have high NPV for excluding NASH.
MRE> 3kPa has highest PPV for NASH.

ABSTRACT FINAL ID: LB-4

TITLE: Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

- Background:
  - Alcoholic hepatitis has very high short-term mortality.
  - Granulocyte-colony stimulating factor (G-CSF) induced bone marrow-derived stem cells improve survival in alcoholic hepatitis.
  - N-Acetyl Cysteine (NAC) could have a potential therapeutic role in the treatment of acute alcoholic hepatitis.
- Aim:
  - To assess efficacy of combined G-CSF and NAC therapy in improving outcomes in patients with severe alcoholic hepatitis
- Methods:
  - Fifty-two patients with severe alcoholic hepatitis were randomized
  - Standard medical therapy plus G-CSF at the dosage of 5 μg/kg subcutaneously every 12 hours for 5 consecutive days (Group A; n=15)
  - Standard medical therapy plus G-CSF and intravenous NAC (day 1: NAC at 150, 50, and 100 mg/kg in 250, 500, and 1000 ml of 5% glucose solution over 30 minutes, 4 hours, and 16 hours, respectively; days 2 through 5: 100 mg/kg/day in 1000 ml of 5% glucose solution) (Group B; n=17)
  - Standard medical therapy alone (Group C; n= 20).
  - The primary outcome was 90-day survival.
  - The secondary outcomes were mobilization of CD34+ cells at day 6; Child Turcotte Pugh (CTP), model for end stage liver disease (MELD), and modified discriminant function (mDF) scores until day 90



- Results:
  - There was a significantly better survival in groups A and B as compared to group C (86.7% vs. 30.0%, P=0.002; and, 64.7% vs. 30.0%, P=0.035, respectively) at day 90;
  - Survival was similar in group A and B.
  - There was a statistically significant increase in the CD34+ cells (P=0.000) after 5 days in both G-GSF and combination therapy arms both when compared to controls as well as baseline.
  - There was a significant reduction in median delta change % in mDF at 1, 2 and 3 months; in MELD at 2 and 3 months and in CTP at 3 months in group A as compared to group C (P<0.05).
  - There was a significant reduction in median delta change % in mDF at 3 months and in MELD at 2 months in group B as compared to group C (P<0.05).
  - There was no significant difference in the frequency of various complications in different groups.

- Conclusions:
  - G-CSF improves survival in patients with severe alcoholic hepatitis.
  - The use of G-CSF led to mobilization of hematopoietic stem cells and improved liver function.
  - The use of NAC was not found to have any additional benefit compared to G-CSF.

LB-1 Cenicriviroc versus placebo for the treatment of non-alcoholic steatohepatitis with liver fibrosis: Results from the Year 1 primary analysis of the Phase 2b CENTAUR study

- Background:
  - Cenicriviroc (CVC), an oral chemokine receptor CCR2/5 antagonist, has potent anti-inflammatory and antifibrotic activity in animal models of acute and chronic liver diseases.
  - Its efficacy and safety as a treatment for non-alcoholic steatohepatitis (NASH) and liver fibrosis are being evaluated in adults at increased risk of progression to cirrhosis (CENTAUR; NCT02217475).

- Methods:
  - Phase 2b, randomized, double-blind, placebo-controlled, ongoing 2-year multinational study
  - Primary analysis at Year 1.
  - Subjects with histologically defined NASH, a non-alcoholic fatty liver disease activity score (NAS) ≥4, liver fibrosis (stages 1–3 NASH CRN), and diabetes or metabolic syndrome (MetS)
  - Randomized to CVC 150 mg QD or placebo.
  - NAS, resolution of steatohepatitis, and fibrosis stage were assessed on Year 1 liver biopsies.
  - Markers of systemic inflammation, treatment-emergent adverse events (TEAEs), and laboratory abnormalities were evaluated.

- Results:
  - 289 subjects were randomized: 53% female; 52% diabetes
  - NAS ≥5; 67% fibrosis stage 2–3.
  - Mean BMI (SD) was 34 kg/m2 (6.5).
  - Improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis was obtained in significantly more CVC-treated subjects than placebo overall (p=0.023) and in subgroups with histologically advanced disease characteristics.
  - Improvement in fibrosis by 2 stages was observed in 11 subjects (8 CVC; 3 placebo).
  - Seven subjects progressed to cirrhosis (2 CVC; 5 placebo).
  - IL-6, hs-CRP, and fibrinogen levels were significantly decreased with CVC vs. placebo.
  - Drug-related, clinical TEAEs of Grade ≥2 severity occurring in ≥2% of subjects were fatigue (2.8%) and diarrhea (2.1%) for CVC; headache (3.5%) for placebo.
  - There were no differences in laboratory abnormalities or premature discontinuations between CVC and placebo.

- Conclusions: In the ITT population, CVC was well tolerated and resulted in twice as many subjects achieving ≥1 stage improvement in fibrosis and no worsening of steatohepatitis vs. placebo, after only 1 year of treatment. Importantly, greater treatment benefits were observed in subjects with higher disease activity and stage.

ABSTRACT FINAL ID: 201

TITLE: The weighted effect of non-alcoholic steatohepatitis on hepatocellular carcinoma risk: A meta-analysis

- Background:
  - Nonalcoholic steatohepatitis (NASH) is the second leading indication for liver transplantation (LT) in the United States.
  - Hepatocellular carcinoma (HCC) has increased four-fold in those with NASH cirrhosis awaiting LT.
  - NASH may also affect HCC risk in patients without cirrhosis.
- Objectives:
  - To assess the impact of NASH on the development of HCC in adult patients with and without cirrhosis using the available literature to guide management decisions.
- Methods:
  - Published studies were identified by searching MEDLINE, Scopus, Science Citation Index, AMED, and the Cochrane Library through April 2016.
  - Effect magnitude was determined by calculating DerSimonian and Laird random effects odds ratios to obtain aggregate estimates of effect size and 95% confidence intervals. Between-study variability and heterogeneity were assessed

- Main results:
  - After reviewing 734 citations, we included 19 studies with 168,571 participants.
  - Eighty-six percent of included subjects had cirrhosis.
  - The prevalence of HCC in aggregate was 12.4%.
  - NASH subjects without cirrhosis were at significantly greater odds of developing HCC than non-cirrhotic patients of other etiologies (OR 2.61, 95% CI 1.27-5.35, p=0.009).
  - When examining patients both with and without cirrhosis, those with NASH as the underlying liver disease did have an increased risk of HCC.
  - This effect was not statistically significant (OR 1.43, 95% CI 0.77-2.65, p=0.250) when compared directly to a composite of all other etiologies of liver disease.
- Conclusions:
  - Taken as an isolated etiology, individual studies suggest NASH is associated with HCC risk when compared to other etiologies of liver disease.
  - In pooled analysis, we found that in non-cirrhotic patients, those with NASH have a higher risk of HCC compared to other etiologies of liver disease.

ID: 1125

TITLE: Intra-Gastric Balloon (IGB): an endoscopic treatment option for obesity and NAFLD

- Background:
  - Endobariatric devices, including intra-gastric balloons (IGBs), may provide an alternative option for weight control.
- Methods:
  - The outcomes following IGB placement in obese patients with insulin resistance from 2005 till 2015 at a tertiary hospital retrospectively examined.
  - Clinical, anthropometric and biochemical data were routinely recorded and examined at baseline, and after IGB removal at 6 months.

Clinical Parameter	Patient numbers (N=135)
Age (years), mean ± SD	47.1 (12.2)
Sex (M/F)	39 (29%)/96 (71%)
Ethnicity -Caucasian -Other	 89 (66%) 46 (34%)
Metabolic syndrome features	60/134 (45%); T2DM 39 (29%)
Weight (kg), mean ± SD	117.9 (22.0)
BMI (kg/m^2), mean ± SD	41.7 (6.6)
Waist circumference (cm), mean ± SD	124.2 (13.6)
Fasting BSL (mmol/L), mean ± SD	6.0 (2.7)
Fasting insulin (mIU/L), mean ± SD	136.0 (169.0)
HOMA-IR, median (range)	3.6 (2.1-5.9)

Table 1: Baseline characteristics

Results

Clinical Parameter	Baseline	6 months	Mean difference	*p*-value
Weight (kg)	**117.9**	**106.6**	**11.3**	**<0.01**
BMI (kg/m²)	**41.7**	**37.6**	**4.1**	**<0.01**
Waist circumference (cm)	**124.2**	**101.1**	**23.1**	**0.04**
Fasting BSL (mmol/L)	6.0	5.4	0.6	0.12
Fasting insulin (mIU/L)	136.0	96.5	39.5	0.12
HOMA-IR	**3.6**	**2.6**	**1.0**	**0.03**
ALT (IU/L)	**38.9**	**31.0**	**7.9**	**<0.01**
AST (IU/L)	35.1	32.8	2.3	0.11
GGT (IU/L)	**62.6**	**39.1**	**23.5**	**<0.01**
Fasting cholesterol (mmol/L)	4.8	5.1	-0.3	0.08
Fasting LDL (mmol/L)	2.7	2.8	-0.1	0.09
Fasting HDL (mmol/L)	1.2	1.5	0.7	0.39
Fasting triglycerides (mmol/L)	1.8	1.4	0.4	0.22

Table 2: Clinical outcomes at 6 months

Results: Side Effects

Reported side effects	Number of patients
Nausea and vomiting	28 (20.7%)
Abdominal pain	8 (5.9%)
Abdominal bloating/flatulence	16 (11.9%)
Constipation or diarrhoea	6 (4.4%)
Gastro-oesophageal reflux	9 (6.7%)
Erosive damage to stomach lining	2 (1.5%)
Deflation or displacement of IGB	1 (0.7%)
Gastrointestinal obstruction	1 (0.7%)
Premature removal	14 (10.4%)

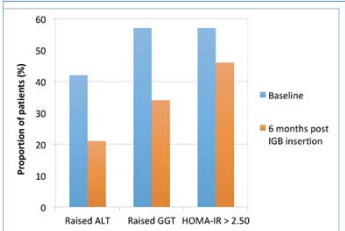


Figure 1: Proportions of patients with abnormal transaminases compared with HOMA-IR at baseline and 6 months.

Conclusions:

IGB provides an effective, alternative non-surgical means of inducing weight loss for the management of obesity and obesity-associated liver dysfunction over the short term.

Improvements in insulin resistance and hepatic transaminases correlated with greater degrees of weight change.

ID: 1090 Impact of liver histology on the post-operative morbidity and mortality of bariatric surgery

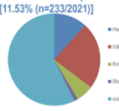
- Background:
  - Bariatric surgery has become a common treatment option.
  - Post-operative morbidity and mortality of these patients with more severe liver disease is poorly known.
  - The true impact of NASH on post-operative complications is unknown.
- Aim:
  - Evaluate the impact of liver histology on the post-operative morbidity and mortality of bariatric surgery.
- Methods: Patients operated of bariatric surgery were included and prospectively followed.
  - Clinical, biological and histological data as well as post-op morbidity within 30 days were collected.
  - The studied histological data that could impact post-op morbidity were: significant fibrosis (≥F2 METAVIR), cirrhosis, NASH and severe NAFLD (NAS≥5).
  - If the distribution of the type of surgery was different between groups, complications were studied for each surgical procedure (gastric banding, sleeve gastrectomy, and bypass).

Results

Characteristics of the cohort n = 2021

Age (years), mean ± SD	41,15 ± 11,57
Gender M / W (%)	493/1528 (75,6)
Follow-up (days), median (IQR)	1534 (721-2316)
Diabetes %	30,3%
BMI (kg/m²), mean ± SD	47,89 ± 8,07
ALT (UI/l), mean ± SD	31,95 ± 21,07
GGT (UI/l), median (IQR)	30 (20-47)
Fibrosis F0	67,54
F1	17,56
F2	2,82
F3	1,04
F4	1,39
NASH, n (%)	161 (7,97)
Steatosis (%), median (IQR)	25 (5-50)
Score NAS, median (IQR)	1 (1-3)

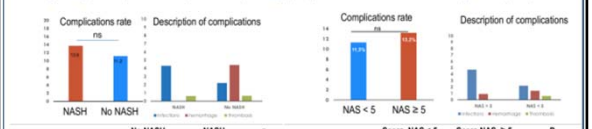
Distribution of complications among all complications [11.53% (n=233/2021)]



Patients with or without complications

Clinical data	No Complication	Complication	p
Age mean ± SD	40,9±11.7	42,9±10.1	<0,01
BMI moy ± SD	47,2±9,1	50,5±7,2	<0,01
gender % (men)	23,9±	27,9	0,18
Cardiovascular risk			
HTA %	56,6	61,8	0,14
Diabète %	29,8	35,2	0,12
Dyslipidémie %	57	61,3	0,18
Histology			
Fibrosis	0,32±0,7	0,52±0,9	<0,01
≥F2 (metavir) %	5,9	11,2	<0,01
Stéatosis % (median)	25	30	<0,01
NAS	1,8±1,5	2±1,5	0,054
Biological data	**No Complication**	**Complications**	**p**
AST IU/L	25,6	25,6	0,08
ALT IU/L	31	32	0,7
Total Bilirubin mg/L	4,7	4,8	0,07
GGT IU/L	30	32	0,6
PAL IU/L	144±76	179±58	<0,01
Ferritin UI/L	109	129	<0,01
Glucose mg/dL	98	100	0,55
HbA1c %	6,3±1,4	6,5±1,5	<0,01
1/QUICKI	3,19±0,40	3,32±0,52	0,01
LDL mmol/L	3,02	3,08	0,39
Cholesterol Total	5	5,2	<0,01
Triglycerides g/L	1,7±1,51	1,81±1,13	0,02

Morbidity: Early post-operative complications (<30 days), impact of NASH and Nafld Activity Score (NAS)

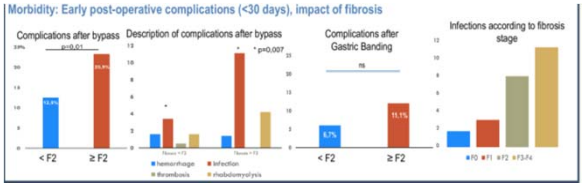


	No NASH n = 1683	NASH n = 161	p
Age (year), mean ± SD	40,69 ± 0,28	46,39 ± 0,90	<0,001
BMI (kg/m²), mean ± SD	47,86 ± 0,20	48,18 ± 0,63	0,5
Diabetes (%)	27,2	65	<0,001
Steatosis (%), mean ± SD	28,31 ± 0,61	57,12 ± 1,98	<0,001
METAVIR, median (IQR)	0 (0-0)	1 (0-2)	<0,001

	Score NAS < 5 n = 1702	Score NAS ≥ 5 n = 106	P
Age (years) mean ± SD	40,75 ± 0,29	46,53 ± 1,12	<0,001
BMI (kg/m²), mean ± SD	47,87 ± 0,20	47,28 ± 0,77	0,7
Diabetes %	27,4	72,3	<0,001
Steatosis(%), mean	28,57 ± 0,60	68,07 ± 1,98	<0,001
Score NAS, mean ± SD	1,59 ± 0,03	5,47 ± 0,11	<0,001

NASH (13.6 vs. 11.2% p=0.36) and NAS≥5 (13.2 vs. 11.3% p=0.53) were not associated with morbidity.

Morbidity: Early post-operative complications (<30 days), impact of fibrosis



Histological lesions associated with morbidity:
Cirrhosis (25 vs. 11.4% p=0.04)
Fibrosis ≥ F2 (after bypass) (23.3% vs. 12.5% p=0.01).

Infection was the most frequent complication and its incidence increased according to the severity of fibrosis (F0: 1.8%; F1: 3.1%; F2: 8.1; F3-F4: 11.4%).

Multivariate analysis: Morbidity after bariatric surgery.

	Odds ratio		P
Age	1,02	1,003-1,3	0,012
BMI	1,04	1,02-1,06	<0,001
Fibrosis≥F2	1,90	1,16-3,11	0,010
Steatosis≥30%	1,54	1,15-2,08	0,004

Conclusion

- Morbidity was associated with higher age, BMI, fibrosis and steatosis.
- Even though morbidity was higher with fibrosis and severe liver disease, the 5-year survival in the overall cohort was excellent.

Summary

- Increasing prevalence of NASH
- Modest alcohol use does not benefit NASH
- Metabolomics is a promising new tool for diagnosis
- Advanced imaging technologies may play a greater role in diagnosis
- Promising new anti-inflammatory and anti-fibrotic therapies
- Potential role of G-CSF in severe alcoholic liver disease
- Increased risk of liver cancer in non-cirrhotic NASH