The Fatty Liver in Underwriting

Case:
JD – Male, Nonsmoker – $50,000
DOB 8/4/65
Hx of splenectomy age 9

1995 presented with ALT 200, AST 160 Alk Phos 300
Dx?

Had Cholecystectomy and at operation liver WNL and U/S showed thickened GB, normal liver

2002 presented with TC 270, TC/HDL 7, Triglycerides 200, Build 5.6.250
AST 40, ALT 50, GGT 200
U/S shows fatty liver changes
FHx DM, Renal CA, AAA CVA

Rate for liver low moderate high?

2009

ALKP	**171**	**u/L**	**HIGH**	**50 - 136**
ALT	**97**	**u/L**	**HIGH /**	**30 - 65**
AST	**145**	**u/L**	**HIGH /**	**15 - 37**
TP	**8.7**	**g/dl**	**HIGH**	**6.4 - 8.2**
ALB	**3.5**	**g/dL**		**3.4 - 5.0**

Rate in 2009 – low moderate high?

This PI had Fatty liver, ETOH abuse, HCV
This highlights the spectrum of Fatty Liver Disease. It is imperative, in Fatty Liver – or in cases where one feels fatty liver is the cause of elevated enzymes, to attempt to evaluate the increased mortality factors.
By far most fatty liver will be caused by metabolic syndrome risk factors. The more numerous or more uncontrolled (especially hyperglycemia, waist circumference or ETOH high moderate), the more mortality will be associated.

"Non-alcoholic Fatty liver disease"
Described in 1980
Only 20 patients were in this cohort. All denied Alcohol use. All but one of the patients were obese. All had disease indistinguishable from Alcoholic liver disease
In Fact – 3 had HGsAg + and HCV probably present in many others

In 2002 2.9% of liver transplants done in NAFLD – at that time prevalence noted to be 20%
In 2006 a study showed a 25-30% prevalence of NAFLD – 3-5% had NASH and 10% proceeded to Cirrhosis.
18 year overall mortality was 2.7% in NAFLD, but 17.5% in NASH

#1 cause – CV, #2 malignancies, #3 hepatic issues

NOW
NAFLD is up to 30% of population – NASH (nonalcoholic steatohepatitis may be up to 15% on these
The majority of population with NAFLD has NORMAL enzymes

In fact NHANES shows 6% prevalence abnormal enzymes – 30% of this will normalize on a second sample – may or may not have NAFLD
Estimates are that 39-55% of persons with elevated hepatic enzymes have NAFLD
In a group of persons drinking 20-50 Gm. of alcohol a day, Obesity is a stronger predictor of steatosis than is alcohol.

ALD Prevalence may be up to 5-7%
This will be high ETOH users, usually in the 60-80 up Grams a day of ETOH.

The majority of cases of fatty liver in the US seem to have a complex, multifactorial basis.
Fatty liver is associated with cardiovascular and higher overall mortality.
The mortality is driven by the degree of the cause

Lab
NAFLD early
AST<ALT – mild <2 x normal or WNL
GGT up to 3 X
AP up to 1.5 X
ALD Early
AST<ALT mild <2 X Normal or WNL
ALD Later
AST>ALT >2 strong suggest
GGT up to 3 X
AP up to 1.5 X

Table 2 Category of Liver Disease by Predominant Serum Enzyme Abnormality

Test	Liver Disease Category		
	Hepatocellular	Cholestatic	Infiltrative
AST, ALT higher than alkaline phosphatase level	Typical	—	—
Alkaline phosphatase higher than AST, ALT levels	—	Typical	—
Elevation of alkaline phosphatase with near-normal AST, ALT levels	—	Typical	Typical

ALT, alanine aminotransaminase; AST, aspartate transaminase.
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Other Causes
Prior drug toxicity or infection or metabolic issue

Völzke H. Multicausality in fatty liver disease

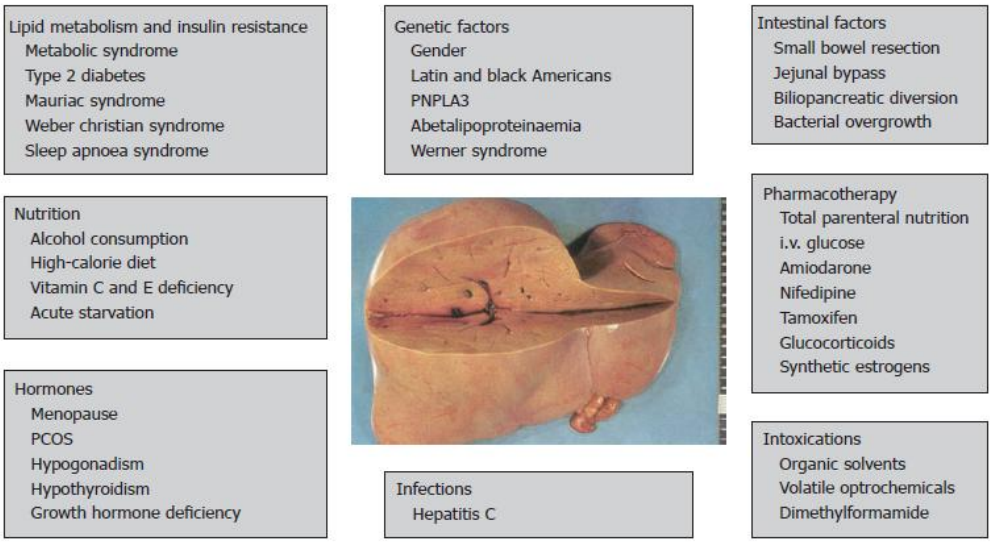

Figure 1 Risk factors for fatty liver disease[17,32,72,82-87]. PNPLA3: Patatin-like phospholipase domain-containing protein 3; PCOS: Polycystic ovary syndrome.

ETOH
NAFLD = < 20 g per day ETOH – but practically consider up to 40 Gm. unless one feels significant ETOH abuse exits
ALD = typically > 40-80 g per day

Table 84-1 Alcohol Content of Various Beverages

BEVERAGE	ALCOHOL CONTENT	SERVING SIZE	AMOUNT OF ALCOHOL	Daily Intake Needed to Exceed Threshold for Alcoholic Liver Disease*	
				MEN	WOMEN
Beer	5%	12 oz	13.85 g	3-6 cans	1.5-3 cans
Wine	12%	4 oz	10.7 g	4-8 glasses	2-4 glasses
Fortified wine	20%	4 oz	17.8 g	2-4 glasses	1-2 glasses
Hard liquor	40%	1.5 oz	13.4 g	3-6 drinks	1.5-3 drinks

*Alcohol intake of 40-80 g/day for men and 20-40 g/day for women for 10 years.

Probably most are mixed and some – like our case – have several issues

SHIP study:
Shows that "Non-alcoholic" FLD is a mix of ETOH and other metabolic factors.
All factors work together to drive Fibrosis.
Fibrosis Drives mortality

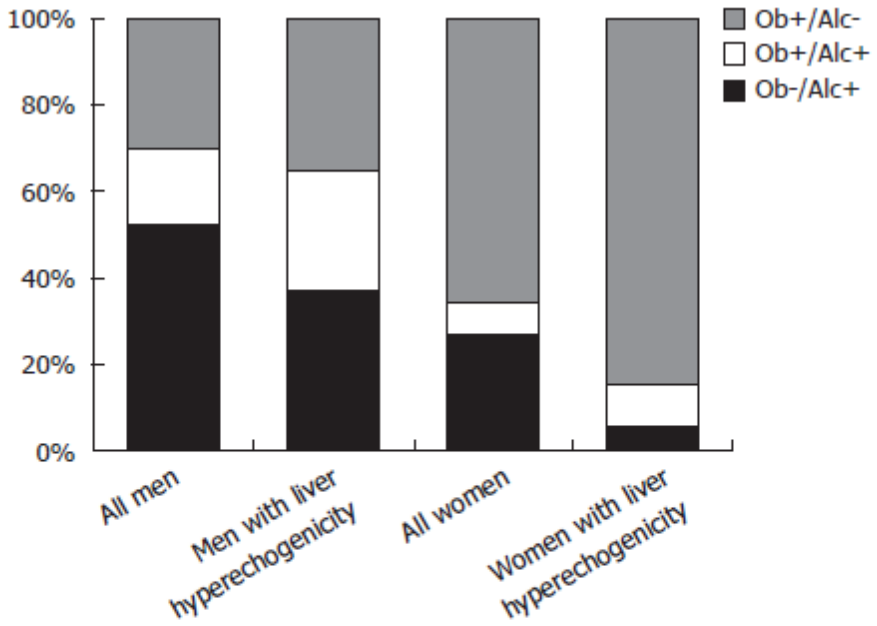

Figure 2 Obesity and alcohol consumption in the general population of Northeast Germany. Data are taken from the population-based Study of Health in Pomerania. The columns indicate the proportions of obesity (Ob; body mass index > 30 kg/m²), harmful alcohol consumption (Alc; daily alcohol consumption > 20 g in women and > 30 g in men), the combined presence of both risk factors in all subjects (1122 men, 781 women) and subjects with a hyperechogenic pattern on liver ultrasound (535 men, 276 women), in whom at least one of both risk factors was present.

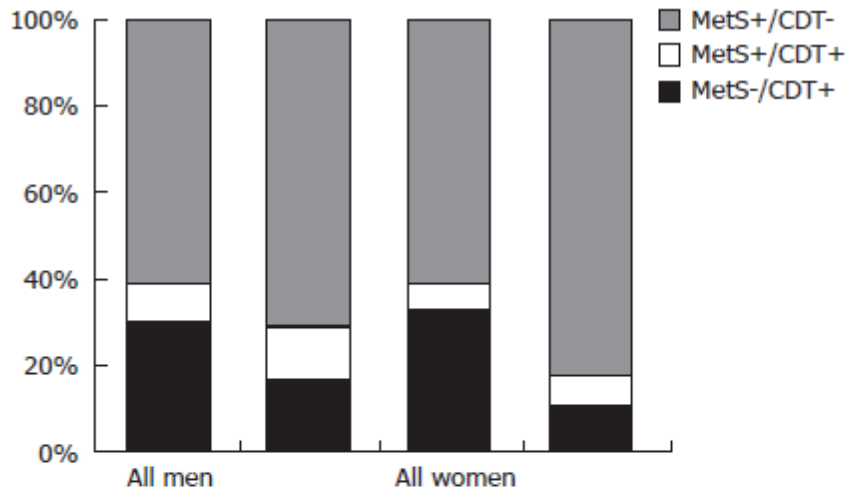

Figure 3 Metabolic syndrome and increased serum carbohydrate-deficient transferrin in the general population of Northeast Germany. Data are taken from the population-based Study of Health in Pomerania. The columns indicate the proportions of metabolic syndrome (MetS), increased serum carbohydrate-deficient transferrin (CDT > 6%), the combined presence of both risk factors in all subjects (970 men, 685 women) and subjects with a hyperechogenic pattern on liver ultrasound (486 men, 288 women), in whom at least one of both risk factors was present.

Diagnosis of FLD:

Biopsy is gold standard – But liver Bx is notoriously spotty in making a Dx – minimal tissue on most samples, and event with solid tissue samples the NPV for NASH may be as low as 0.74
But U/S has 90% Sn and 80% Sp

Is FLD a cause of significant mortality?

NAFLD

There is still a lack of clarity concerning the long-term outcome and severity of non-alcoholic fatty liver disease (NAFLD). Results of a study recently conducted by the National Health and Nutrition Examination Survey (NHANES) showed that patients with NAFLD diagnosed 30 years ago did not experience decreased survival when compared with persons without NAFLD. But questions arise about the diagnostic methods in this study and the consequences for daily practice. Is NAFLD really a disease, and what is the diagnostic method of choice?

A Minnesota study with data from patients Dx in 1980 – 2000 showed over mean F/U of 8 years a MR of 134% vs. general population – The major risk factor was some fibrosis or some hyperglycemic issue

Another study from China showed annual incidence of NAFLD to be 9.1%

Metabolic syndrome predicted progression here.

Annual mortality was 0.54% in NAFLD vs. 0.18% in a randomized group of non-affected persons

ALD is more significant – has an ongoing severe toxin that affects hepatic cells in multiple ways via oxidative hypoxic stress
Also risk of non-hepatic death is elevated

For patients with alcoholic pure steatosis
The 5-year cirrhosis risks were 6.9% (95% CI: 3.4-12.2%)
5-year mortality risks were 16.7% (95% CI: 11.3-24.2%)

For patients with alcoholic steatohepatitis
The 5-year cirrhosis risks were 16.0% (95% CI: 7.8-26.8%)
5-year mortality risks were 25.1% (95% CI: 15.7-38.9%)

So – Two issues are apparent
How to Dx ETOH use and how to Dx Fibrosis
In underwriting we need to pull out high ETOH abusers with the highest risk.
Then need to assess which of the other cases have the most metabolic syndrome factors (risk for fibrosis) or need to Dx actual fibrosis.
FLD due to ETOH or metabolic or combination may not need to be rated highly if low fibrosis.

Alcohol abuse in US

Twelve-month prevalence of DSM-IV alcohol abuse by age, sex, and race-ethnicity: United States, 2001–2002 (NESARC)*.

[abusdep1.htm, dated 01/05]

Sociodemographic characteristic	Male			Female			Total		
	%	S.E.	Population estimate[a]	%	S.E.	Population estimate	%	S.E.	Population estimate
Total									
Total	6.93	0.28	6906	2.55	0.16	2762	4.65	0.18	9668
18–29	9.35	0.61	2110	4.57	0.39	1041	6.95	0.39	3151
30–44	8.69	0.49	2742	3.31	0.28	1080	5.95	0.31	3822
45–64	5.50	0.43	1719	1.70	0.20	566	3.54	0.25	2286
65+	2.36	0.32	335	0.38	0.11	75	1.21	0.15	410

We can screen via isolated markers:
Below the Sn of some markers in high ETOH abuse (average 130 gm. /day use)

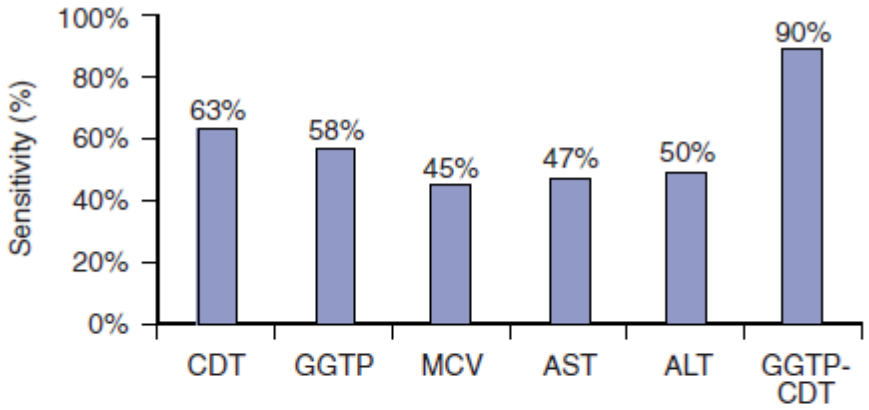

Figure 84-4. The sensitivities of serum levels of carbohydrate-deficient transferrin (CDT), gamma glutamyl transpeptidase (GGTP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GGTP plus CDT in combination and the mean corpuscular volume (MCV) for detecting heavy drinkers for a population of 165 heavy drinkers consuming a mean of approximately 130 g of ethanol per day. The corresponding specificities for the above markers in this group were 98% for CDT, 99% for GGTP, 94% for MCV, 95% for AST, 87% for ALT, and 98% for GGTP plus CDT. (From Niemelä O. Biomarkers in alcoholism. Clin Chimica Acta 2007; 377:39-49, with permission.)

We know that ETOH consumption drives higher mortality in all forms of liver disease. Some studies suggest low mortality in NAFLD in a subset of very low ETOH users (this may be a reflection of the ETOH J curve)
Below is a graph of how ETOH chronic use affects HCV (the other cause of FLD)

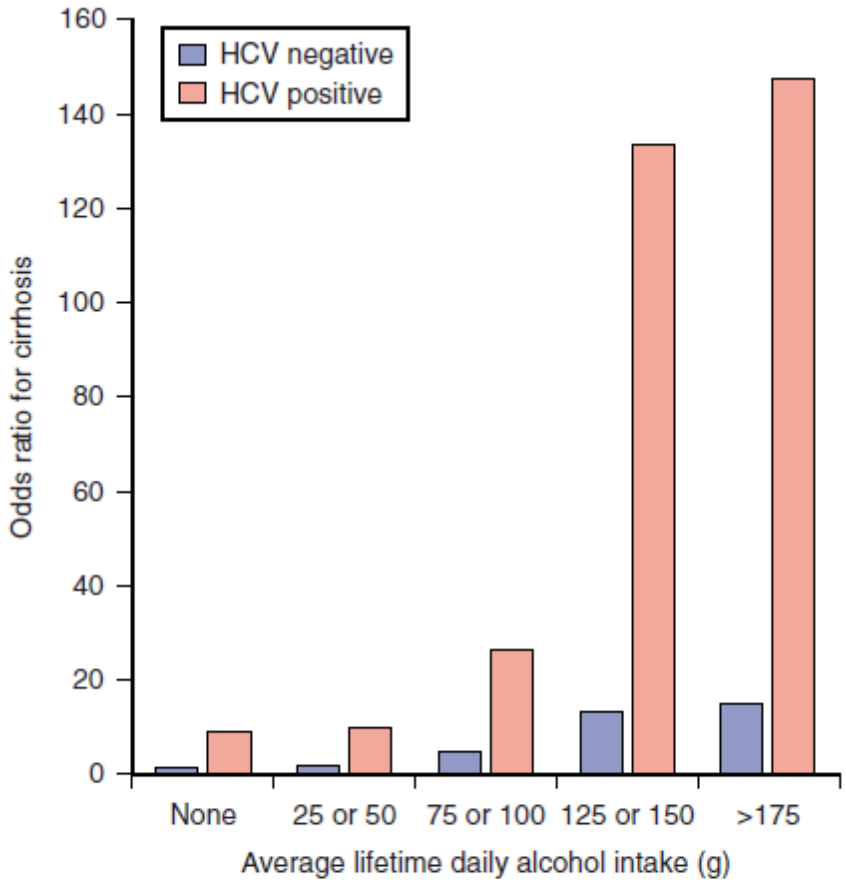

Figure 84-5. Odds ratio for developing cirrhosis in patients who chronically drink varying amounts of alcohol based on the presence or absence of hepatitis C virus (HCV) infection. (Data from Corrao G, Lepore AR, Torchio P, et al. The effect of drinking coffee and smoking cigarettes on the risk of cirrhosis associated with alcohol consumption. A case-control study. Provincial Group for the Study of Chronic Liver Disease. Eur J Epidemiol 1994; 10:657-64.)

But how to pick out ETOH users?

Three common methods based on Labs = CDT, GGT, MCV levels (HDL level is also of use, but is altered by Statin use – Sn similar to MCV and Cliff Titcomb has shown how it can be used in screening already)

Below is a set of data from the SHIP study comparing lab results from all subjects (again, average use is 130 gm. /day in the subjects and non-drinkers

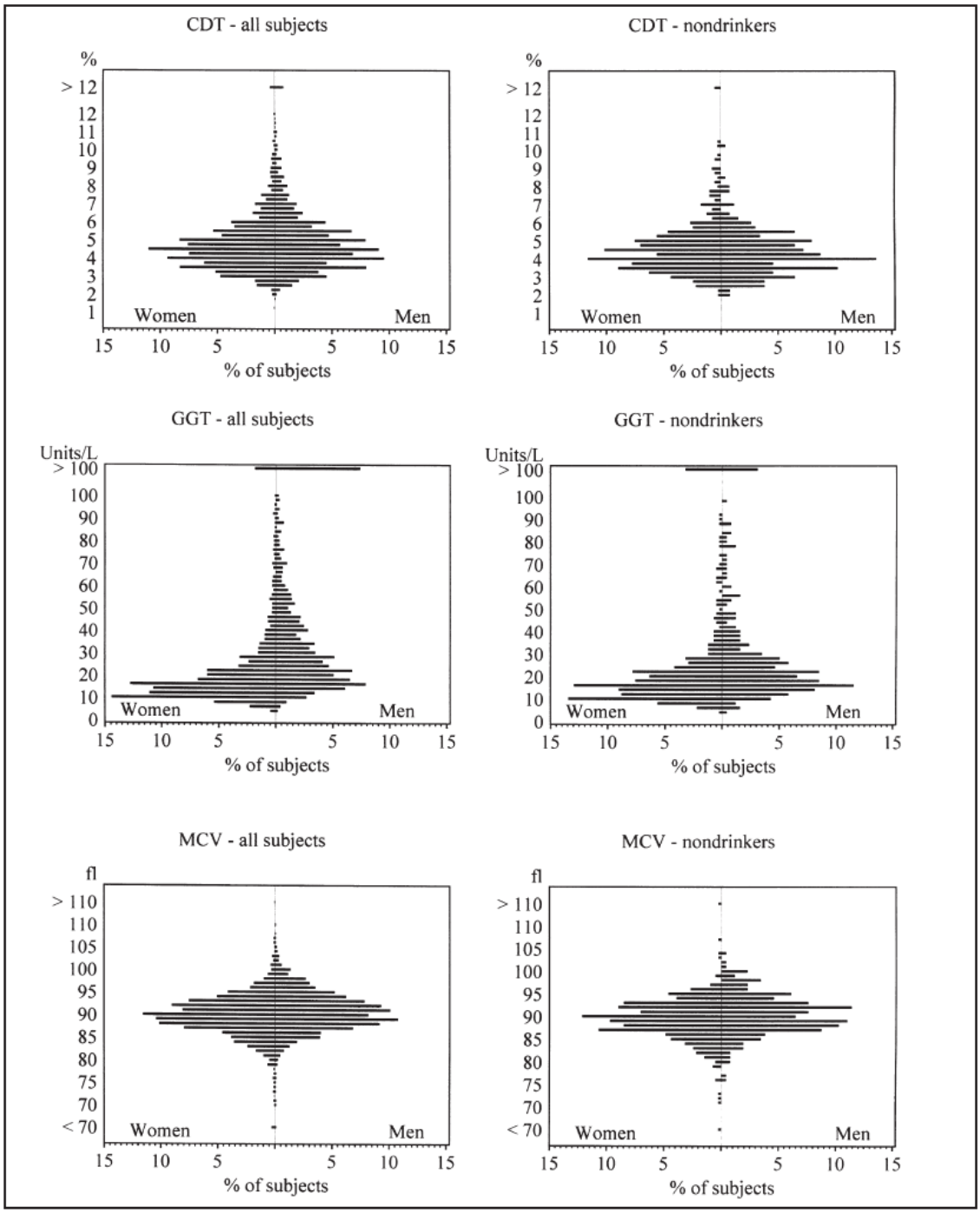

FIGURE 1. Distribution of CDT, GGT and MCV in all and in nondrinking subjects (extreme values are pooled at top/bottom of graph) (SHIP X/1997-V/2001)

There is very little differentiation here.

Onni Niemela has been involved in numerous looks into this issue and points out the use of GGT-CDT combination factor [0.8*ln(GGT) + 1.3*ln(%CDT)].
The combination of GGT-CDT was of better use in separating the heavy drinkers, but not in differentiation moderate from abstainers as well.

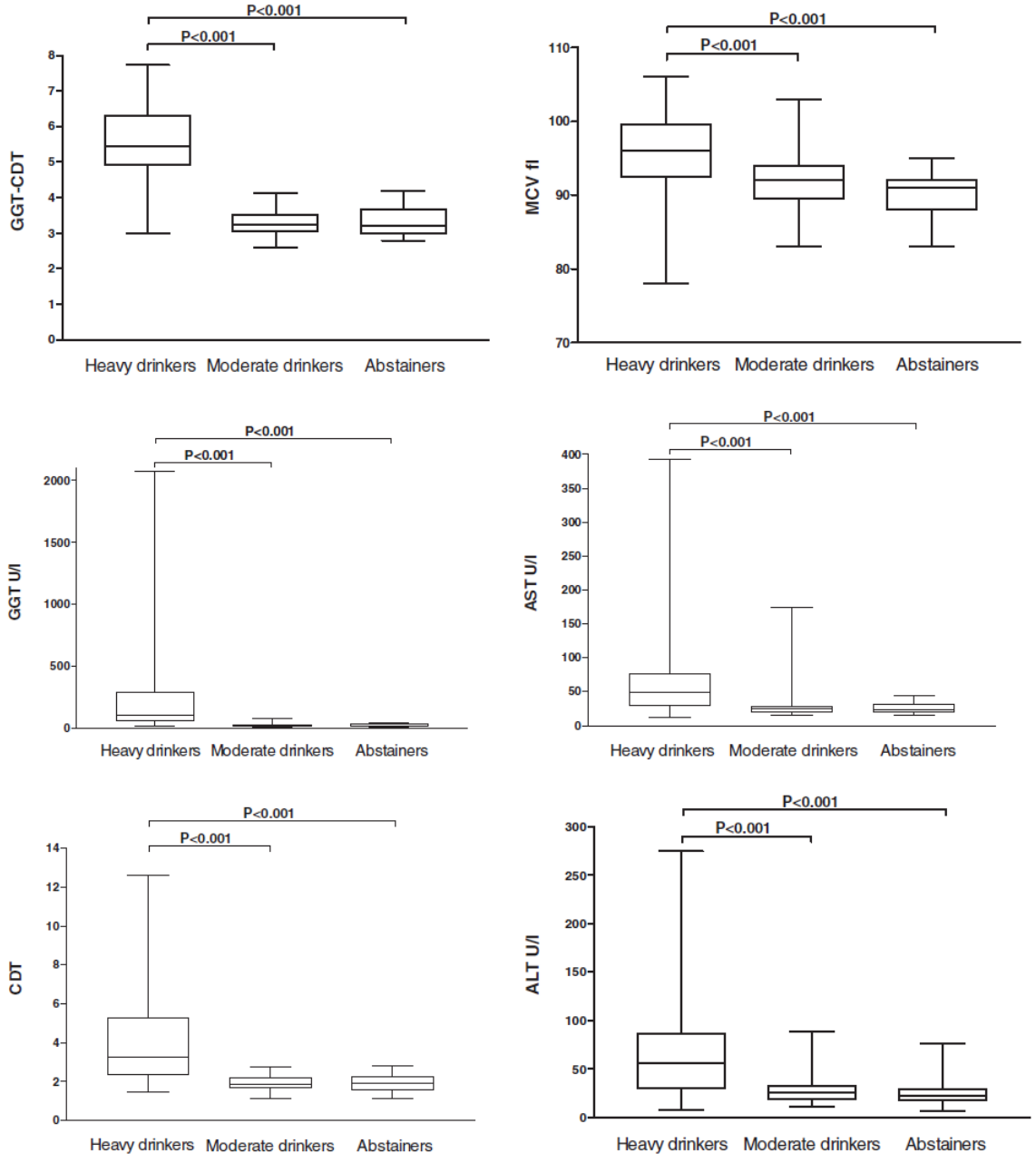

Fig. 1. Box plots of various laboratory markers of alcohol consumption in heavy drinkers, moderate drinkers, and abstainers. Alcohol abusers show significantly higher values than moderate drinkers or abstainers in all comparisons ($P < 0.001$). GGT–CDT, combined marker based on the data from GGT and CDT measurements; GGT, γ-glutamyltransferase; CDT, carbohydrate-deficient transferrin; MCV, mean corpuscular volume; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

This article also gives a set of Sn and SP in table form and how fast values normalized

Table 1. Sensitivities of laboratory markers of alcohol consumption in heavy drinkers, as also divided by gender and liver status, and the specificities, as obtained from the current reference population

			Heavy drinkers			Heavy drinkers with liver disease			Heavy drinkers without liver disease		
	Cut-off		All $n = 165$	Men $n = 140$	Women $n = 25$	All $n = 51$	Men $n = 38$	Women $n = 13$	All $n = 114$	Men $n = 102$	Women $n = 12$
GGT–CDT	Men 4.18	Sensitivity	90	89	96	93	91	100	88	88	91
	Women 3.81	Specificity	98	98	97	98	98	97	98	98	97
GGT U/l	Men 80	Sensitivity	58	56	68	76	79	69	50	48	67
	Women 50	Specificity	99	98	100	99	98	100	99	98	100
CDT %	2.60	Sensitivity	63	65	52	67	71	58	60	62	45
		Specificity	98	100	94	98	100	94	98	100	94
GGT or CDT elevated		Sensitivity	85	86	83	89	91	83	84	84	82
		Specificity	96	98	94	96	98	94	96	98	94
GGT and CDT elevated		Sensitivity	37	38	35	54	59	42	28	28	27
		Specificity	100	100	100	100	100	100	100	100	100
MCV fl	96	Sensitivity	45	46	36	69	70	67	42	44	27
		Specificity	94	94	95	94	94	95	94	94	95
AST U/l	Men 50	Sensitivity	47	43	68	59	53	77	42	40	58
	Women 35	Specificity	95	94	97	95	94	97	95	94	97
ALT U/l	Men 50	Sensitivity	50	49	57	92	100	67	44	43	55
	Women 35	Specificity	87	88	86	87	88	86	87	88	86

Table 2. Correlations between biochemical markers of ethanol consumption, and markers and self-reported ethanol consumption

	GGT–CDT	GGT	CDT	MCV	AST	ALT
GGT–CDT	1					
GGT	0.90***	1				
CDT	0.78***	0.47***	1			
MCV	0.56***	0.58***	0.33***	1		
AST	0.72***	0.66***	0.55***	0.43***	1	
ALT	0.66***	0.68***	0.40***	0.33***	0.85***	1
EtOH g/ previous day	0.45***	0.42***	0.40***	0.37***	0.38***	0.33***
EtOH g/ previous month	0.76***	0.71***	0.59***	0.52***	0.59***	0.50***

***$P < 0.001$.

Table 3. Normalization rates for alcohol markers based on follow-ups of 44 alcoholic patients with supervised abstinence for a period 11 ± 4 days

Marker	Percentages of declining values	Normalization time (days), mean ± SD
GGT–CDT	93	18 ± 9
GGT	84	16 ± 8
CDT	93	16 ± 11
AST	68	13 ± 20
ALT	57	16 ± 19
MCV	20	N.D.

N.D. not determined.
The sensitivities and specificities are expressed as percentages.
GGT–CDT, combined marker based on the data from GGT and CDT measurements.

The prior Svalbard study of a general population shows the PPV of CDT in a general population. This population would be more similar to what we underwrite

Table 1. Sensitivity (Sens), Specificity (Spec), Positive Predictive Value (PPV), and Likelihood-Ratio (LR) for Carbohydrate-Deficient Transferrin (CDT) According to Sex, Different Levels of Self-Reported Alcohol Consumption, and Different Cutoff-Points for the Test. The Svalbard Study 1988–89

Cutoff-points for CDT (units/liter and percentiles)	Cutoff-Points for Daily Intake of Alcohol											
	80-Percentile (30 g/day)				90-Percentile (41 g/day)				95-Percentile (52 g/day)			
	Sens	Spec	PPV	LR	Sens	Spec	PPV	LR	Sens	Spec	PPV	LR
Males (n = 310)												
14 (50)	66.2	53.3	0.29	1.4	65.6	50.8	0.14	1.3	68.8	50.0	0.07	1.4
15 (60)	55.4	62.0	0.29	1.5	53.1	59.6	0.14	1.3	62.5	59.4	0.08	1.3
17 (70)	44.6	62.0	0.29	1.5	40.6	69.1	0.14	1.3	50.0	69.1	0.09	1.6
19 (80)	38.5	80.8	0.36	2.0	34.4	77.9	0.16	1.6	37.5	77.3	0.09	1.7
22 (90)	26.2	91.3	0.46	3.0	18.8	88.2	0.16	1.6	18.8	87.8	0.08	1.5
28 (95)	13.9	96.9	0.56	4.5	12.5	95.4	0.25	2.7	12.5	95.0	0.13	2.5
	80-Percentile (13 g/day)				90-Percentile (15 g/day)				95-Percentile (22 g/day)			
Females (n = 171)												
17 (50)	60.0	43.7	0.22	1.1	52.4	42.3	0.11	0.9	54.6	42.8	0.06	1.0
18 (60)	48.6	53.3	0.21	1.0	42.9	52.4	0.11	0.9	45.5	52.8	0.06	1.0
20 (70)	40.0	71.9	0.27	1.4	33.3	69.8	0.13	1.1	45.5	70.4	0.09	1.5
21 (80)	37.1	75.6	0.28	1.5	33.3	73.8	0.15	1.3	45.5	74.2	0.11	1.8
25 (90)	11.4	89.6	0.22	1.1	9.5	89.3	0.11	0.9	9.1	89.3	0.05	0.9
31 (95)	2.9	94.1	0.11	0.5	4.8	94.6	0.11	0.9	0.0	94.3		

One method to differentiate drinkers is the Bayesian Alcoholism Test –
This looks at 15 clinical and laboratory markers – so is a bit like looking at Insurance Labs and adding clinical APS data

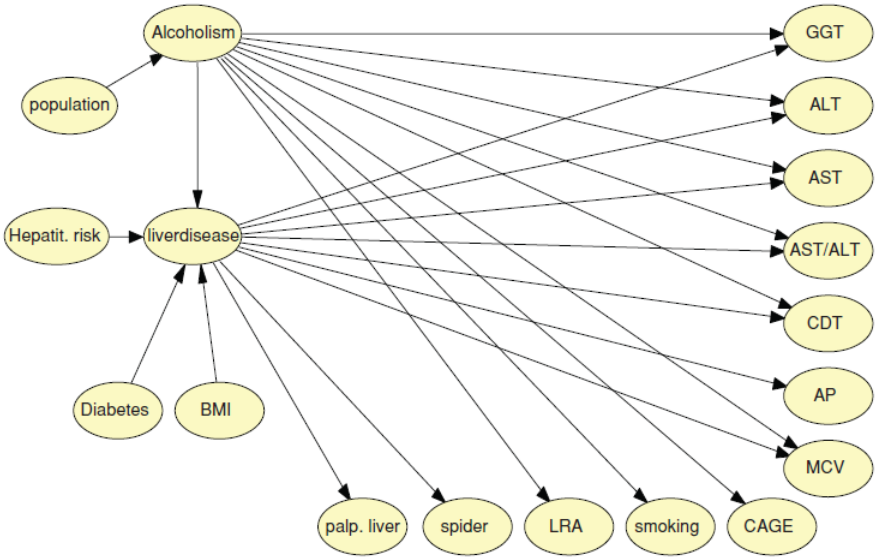

Fig. 1. Network for the Bayesian Alcoholism Test. The *a priori* probabilities for diseases and states (left) are combined with the biochemical (right) and clinical findings (bottom). An arrow going from disease to symptom or biochemical test indicates that the symptom or test is dependent on the disease or state.

The following ROC and tables were done using an 8 item BAT and applying it to a study done by WHO

Table 2. Sensitivity and specificity and likelihood ratios of BAT_8, CDT, GGT and AST for identifying harmful alcohol use (>80 g/day) as compared with controls (<40 g/day)

	Sensitivity	Specificity	Likelihood ratio+	Likelihood ratio−
BAT_8 ($n = 1030$)	**75.8**** (70.8–80.2)	90.0* (87.6–92.0)	**7.6***** (6.0–9.6)	**0.27***** (0.22–0.33)
CDT ($n = 980$)	60.0 (54.4–65.4)	**91.9** (89.6–93.7)	6.2 (4.8–7.9)	0.43 (0.37–0.49)
GGT ($n = 977$)	67.3 (61.8–72.4)	73.7 (70.3–76.9)	4.4 (3.4–5.6)	0.58 (0.52–0.65)
AST ($n = 977$)	45.0 (39.5–50.7)	90.1 (87.6–92.1)	5.8 (4.2–7.9)	0.66 (0.60–0.72)

Bold values: the best result in the table.
*Significant difference BAT_8 compared to GGT at the P level < 0.05.
**Significant difference BAT_8 compared to CDT and AST at the P level < 0.05.
***BAT_8 compared to CDT, GGT and AST. Significant difference at the P level < 0.05.
Values within parentheses: 95% confidence intervals.

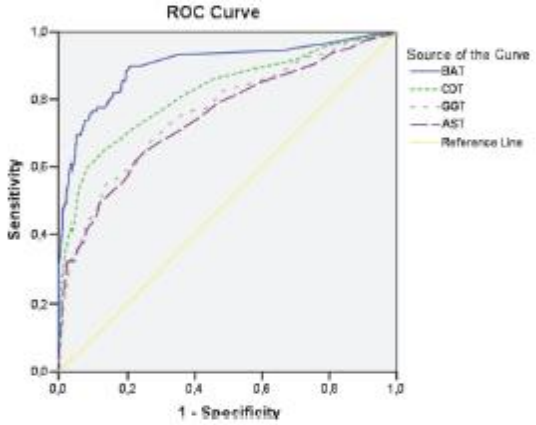

Fig. 2. Areas under the curve of BAT_8, CDT, GGT and AST in the detection of harmful drinkers (>80 g/day) and moderate drinkers (<40 g/day).

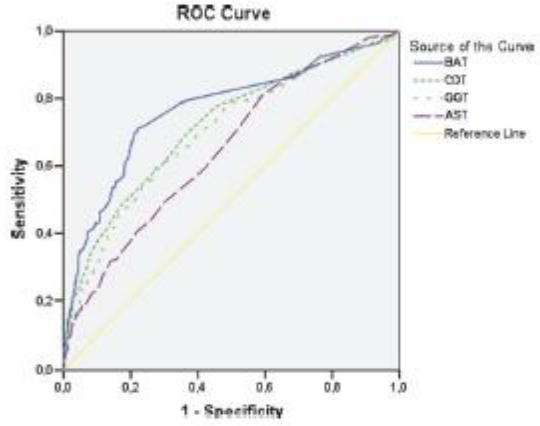

Fig. 3. Areas under the curve of BAT_8, CDT, GGT and AST in the detection of hazardous drinking (40–80 g/day) and moderate drinkers (drinking <40 g/day).

Table 3. Areas under the curve of BAT_8, CDT, GGT and AST for harmful drinkers (>80 g/day) and for hazardous drinkers (≥40 g/day and ≤80 g/day) compared with the control group (<40 g/day)

	AUC comparing harmful users with controls	AUC comparing hazardous use with controls
BAT_8	**0.90**†† (0.87–0.92) standard error 0.011	**0.77**† (0.72–0.80) standard error 0.020
CDT	0.82 (0.79–0.85) standard error 0.016	0.72 (0.67–0.75) standard error 0.021
GGT	0.77 (0.74–0.80) standard error 0.017	0.70 (0.66–0.74) standard error 0.021
AST	0.76 (0.72–0.79) standard error 0.018	0.65 (0.61–0.69) standard error 0.021

Bold values: the best result in the table.
†BAT_8 compared to AST. Significant difference at the P level < 0.05.
††BAT_8 compared to CDT, GGT and AST. Significant difference at the P level < 0.05.
Values within parentheses: 95% confidence intervals.

of hazardous from moderate drinkers. Table 3 summarizes the areas under the curve of both Figs. 2 and 3.

Correlations

Using pooled data from all 1250 males included in the WHO/ISBRA dataset, the amount of drinking demonstrated a significantly better correlation coefficient with BAT_8 0.647 (CI: 0.613–0.678) than with CDT 0.515 (CI: 0.472–0.555), GGT 0.438 (CI: 0.390–0.482) or AST 0.393 (CI: 0.344–0.440) alone (CI: 95%).

DISCUSSION

Background

Fibrosis may be an even better indicator of hepatic issue and presence of fibrosis does correlate to higher mortality groups– it looks at the end organ result.
Fibrosis is also the marker of higher oxidative stress

Fibrotest showed a prevalence of severe fibrosis in up to 15% of a population of DM in one study.

Fibrosis markers via non-invasive means have been numerous.
One =
NAFLD fibrosis score [-1.675 + (0.037 * age [years]) + (0.094 * BMI [kg/m2]) +
(1.13 * impaired fasting glucose/diabetes [yes = 1, no = 0]) + (0.99 * AST/ALT ratio) -
(0.013 * platelet [x109/L]) – (0.66 * albumin [g/dL])]

Two that seem to be holding up are the FibroTest and the Liver Stiffness scan. (FibroScan)

First let's look at a population study looking for the prevalence of fibrosis in the population – it suggested at least 0.7% up to 2.8% - it used Fibrotest and followed with stiffness evaluation and some Biopsies. – The authors felt that Fibrotest was a better evaluator of early fibrosis than hepatic stiffness.
Significant trends are seen. Association of CDT +, metabolic + to fibrosis.
The more "mild" but more pervasive NAFLD seems to end up leading to much of the prevalent fibrosis – 35%
Again note that 29% of HCC (driven by fibrosis) cases in 2006 were "cryptogenic" and felt to be due to NAFLD.
And in 2002 2.9% of liver transplants were due to NAFLD.

Poynard *et al. BMC Gastroenterology* 2010, **10**:40
http://www.biomedcentral.com/1471-230X/10/40

RESEARCH ARTICLE Open Access

Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest)

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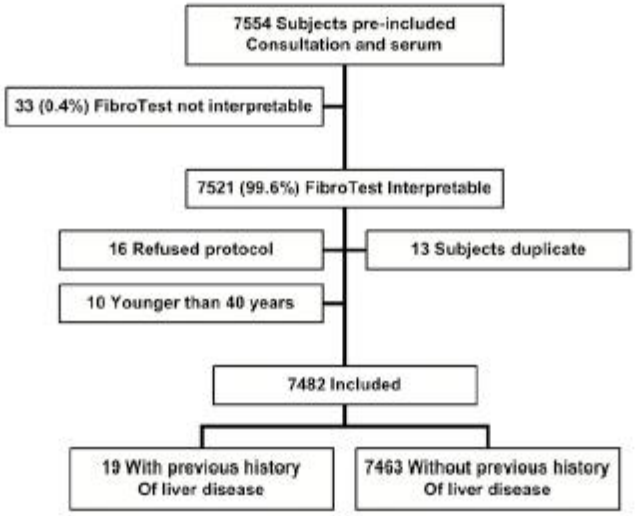

Figure 1 Flow sheet of subjects included.

Table 2: Characteristics of 209 subjects with FibroTest >0.48 (presumed advanced fibrosis) in the population without a history of liver disease

Characteristics	All	Reinvestigated				Not reinvestigated
	Presumed fibrosis	Fibrosis Confirmed	Fibrosis still suspected	Indeterminate	All reinvestigated	
Number of subjects	209	50	27	28	105	104
Prevalence of fibrosis[1]	209/7,463 (2.8%)	100/7,463 (1.3%)	54/7,463 (0.7%)	56/7,463 (0.8%)	100/7,463 (1.4%)	104/7,463 (1.4%)
Cause of liver disease						
Non alcoholic fatty liver disease[2]	98 (47%)	18 (35%)	10 (40%)	13 (46%)	41 (39%)	57 (55%)
Alcoholic liver disease[3]	15 (7%)	4 (8%)	1 (4%)	4 (14%)	9 (9%)	6 (6%)
Non alcoholic and alcoholic	61 (29%)	22 (42%)	11 (44%)	6 (21%)	39 (37%)	22 (21%)
Chronic hepatitis C	6 (3.5%)	4 (8%)	0	1 (4%)	5 (5%)	1 (1%)
Chronic hepatitis B	3 (1.4%)	1 (2%)	1 (4%)	0	3 (3%)	0 (0%)
Hemochromatosis	1 (0.5%)	1 (2%)	0	0	1 (1%)	0 (0%)
Auto-immune hepatitis	1 (0.5%)	0 (0%)	1 (4%)	0	1 (1%)	0 (0%)
No risk factor	25 (12%)	2 (4%)	1 (4%)	3 (11%)	7 (7%)	18 (17%)
Liver complications						
Hepatocellular carcinoma	NP	0 (0%)	0	0	0	NP
Portal hypertension	NP	1 (2%)	0	0	1 (1%)	NP
Stage presumed fibrosis						
Few septa	128 (61%)	26 (50%)	18 (72%)	22 (79%)	66 (63%)	62 (60%)
Many septa	56 (27%)	17 (33%)	6 (24%)	5 (18%)	28 (27%)	28 (27%)
Cirrhosis	25 (12%)	9 (17%)	1 (4%)	1 (3%)	11 (10%)	14 (13%)
Mode of confirmation[4]						
Elastography	NP	47 (90%) (>= 7.1 kPa)	27 (100%) (5kPa-7kPa)	28 (100%) (<5kPa)	102(95%)	NP
Biopsy	NP	3 (5%)	0	1 (4%)	4 (4%)	NP
Endoscopy	NP	1 (2%)	0	0	1 (1%)	NP

[1] Estimated prevalence assuming that the prevalence of advanced ?brosis would be the same in the population of patients not reinvestigated. [2]At least one factor of the metabolic syndrome without alcohol consumption at risk [3]Alcohol consumption at risk self-reported or CDT >1.6% without metabolic factor [4]Possibility of several confirmations for the same subject NP = not performed

Table 3: Predictive values of oriented screening strategies

Strategy	Number subjects	Presumed fibrosis	Confirmed fibrosis
Prevalence fibrosis[1]	*7463*	*209 (2.8%)*	*50 (0.7-1.4%)*
Metabolic factors oriented			
Predictive value			
At least one metabolic factor	3990	163 (4.1%)	40 (1.0%)
None	3473	46 (1.3%)	10 (0.3%)
Odds ratio	7463	3.2 (2.3-4.5)	3.4 (1.7-7.5)
Area under ROC curve	4854	0.69(0.64-0.73)	0.71 (0.59-0.80)
Alcohol-oriented per self-reported consumption			
Predictive value			
>10 g female/20 g male	1686	52 (3.1%)	15 (0.9%)
<= 10 g female/<= 20 g male	5770	157 (2.7%)	35 (0.6%)
Odds Ratio	7456	1.1 (0.8-1.6)	1.5 (0.8-2.8)
Area under ROC curve	7456	0.55(0.51-0.59)	0.52 (0.43-0.60)
CDT oriented			
Predictive value			
CDT>1.6	348	45 (12.9%)	22 (6.3%)
CDT<= 1.6	749	29 (3.9%)	8 (1.1%)
Odds Ratio	1097	3.7 (2.2-6.2)	6.1 (2.6-15.4)
Area under ROC curve	1097	0.72(0.64-0.78)	0.75 (0.67-0.86)
Hepatitis Virus-oriented[2]			
Predictive value			
HBsAg or HCV antibody	36	5 (13.9%)	3 (8.3%)
HBsAg and HCV negative or not done at baseline	7427	204 (2.7%)	47 (0.6%)
Odds ratio	7463	5.9 (1.9-15.6)	15.3 (3.4-50.9)
Transaminases- oriented			
Predictive value			
ALT >= 50 IU/L	513	53 (10.3%)	17 (3.3%)
ALT < 50 IU/L	6950	156 (2.2%)	33 (0.5%)
Odds ratio	7463	5.0 (3.6-7.0)	7.2 (3.8-13.4)
Area under ROC curve	7463	0.72(0.68-0.75)	0.78 (0.72-0.83)
Age-oriented			
Predictive value			
Age > 60 years	2960	156 (5.3%)	42 (1.4%)
Age <= 60 years	4503	53 (1.2%)	8 (0.2%)
Odds ratio	7463	4.7 (3.4-6.5)	8.3 (3.8-19.5)
Area under ROC curve	7463	0.75(0.72-0.78)	0.79 (0.71-0.84)
Gender-oriented			
Male	4113	189 (4.6%)	47 (1.1%)
Female	3350	20 (0.6%)	3 (0.1%)
Odds ratio	7463	8.0 (5.0-13.1)	12.0 (4.0-54.1)

[1] Upper estimated prevalence assuming that the prevalence of advanced fibrosis would be the same in the population of patients not reinvestigated. Lower prevalence assuming that no advanced fibrosis was present among patients not reinvestigated.
[2] This strategy was the standard in the screening centers. Two cases with positive HBsAg detected during reinvestigations of advanced fibrosis were not taken into account. There was one coinfection HCV-HBV.

The following is a similar Japanese study looking at elevated Liver Stiffness in those with Fatty Liver and in those without fatty liver – some had ETOH <20 and some > 20 gm.

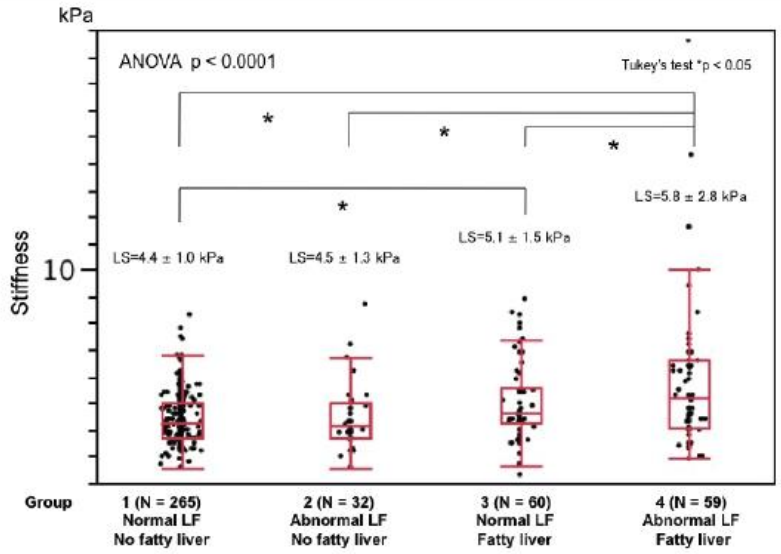

Figure 5 Comparison of liver stiffness among four groups based on liver dysfunction and fatty liver. Liver stiffness significantly differed among these groups. Liver stiffness was highest in Group 4 and that of Group 3 was higher than that of Group 1 according to multiple comparisons (Tukey's test).

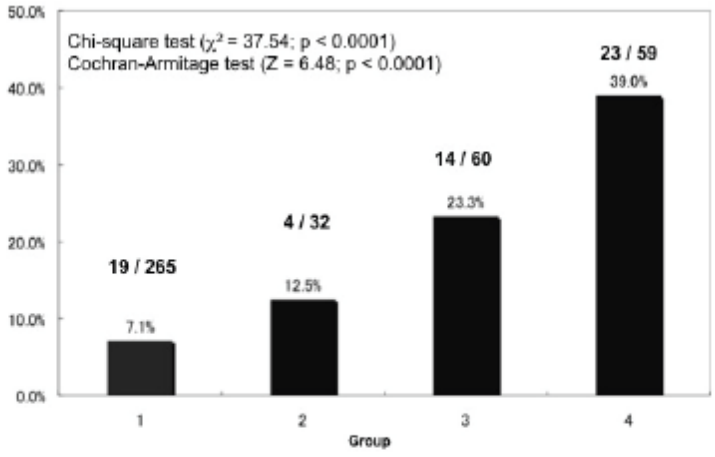

Figure 6 Ratios of individuals in four groups with liver stiffness beyond normal upper limit. Ratios of individuals with LS beyond the normal upper limit significantly differed (χ^2 test and Cochran-Armitage test for trend).

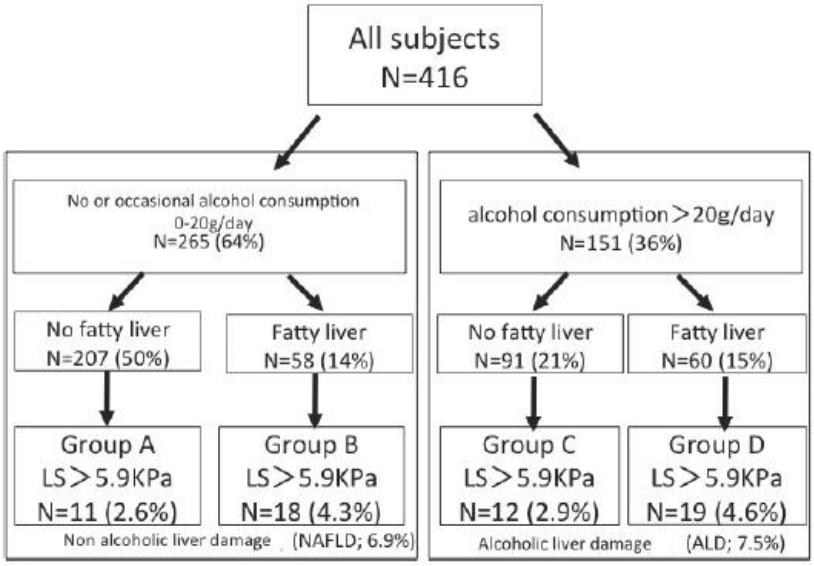

Figure 7 Comparison of liver stiffness among four groups based on alcohol consumption and fatty liver. All participants were assigned to two groups based on alcohol consumption and then each group was further divided into two subgroups with or without fatty liver according to ultrasonography (Groups A, B, C, D). About 7% (6.9% and 7.5%) of all participants had LS above 5.9 kPa among those with NAFLD or ALD regardless of fatty liver.