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(Plenary)

17:50 - 18:10 Approach to Abnormal Liver Function Tests and Fatty Liver

Approach to Abnormal Liver Function Tests & Fatty Liver Disease

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Outlines

- Approach to abnormal liver function tests
  - What are LFTs?
  - Differential diagnosis for different patterns of abnormal LFTs
  - Investigations to order for abnormal LFTs
  - When to refer?
- Non-alcoholic fatty liver disease
  - How common is NAFLD?
  - Natural history of NAFLD
  - How to diagnose NAFLD?
  - Management of NAFLD

1. Approach to Abnormal Liver Function Tests

Case

- 48 years old woman
- History of diabetes mellitus, hypertension and hyperlipidaemia
- BMI 30
- Abnormal LFTs on routine monitoring blood test
  - ALP 110, GGT 120, ALT 82, AST 74, Bilirubin 15

Introduction

- Liver function tests (LFTs)
  - Imprecise term
  - Not all LFTs directly measure "function" of liver
    - Eg. ALT and AST are enzymes released from injured hepatocytes
  - **<u>LFTs loosely refer to tests that evaluate the health status of the liver</u>**

What are "liver function tests"?

- Liver enzymes:
  - ALP
  - GGT
  - AST
  - ALT
- Portal hypertension:
  - Platelets
- Synthetic functions:
  - INR
  - Albumin
- Metabolise/detoxify:
  - Bilirubin
  - Indocyanine green clearance
- Storage:
  - Glucose

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Patterns of Abnormal LFTs

- Hepatitic
  - Raised ALT, AST
- Cholestatic
  - Raised ALP, GGT

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Hepatitic pattern

- Raised ALT and AST

  Catalyse transfer of alpha-amino groups to alpha-keto group

- Transaminases are **sensitive indicators of liver cell injury**

- **ALT more specific** than AST

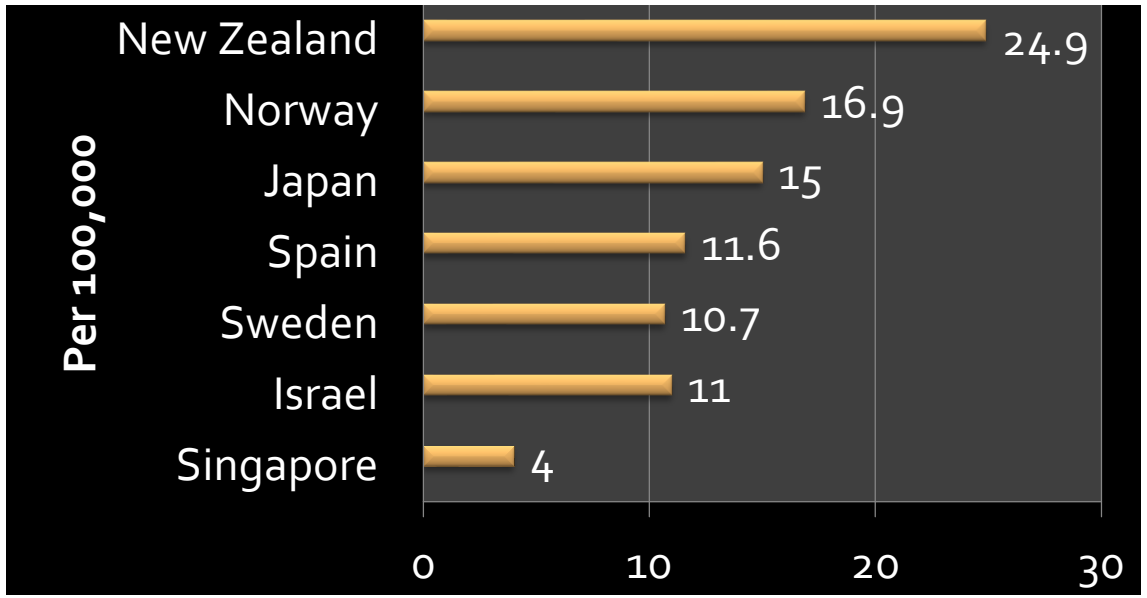
ALT and AST

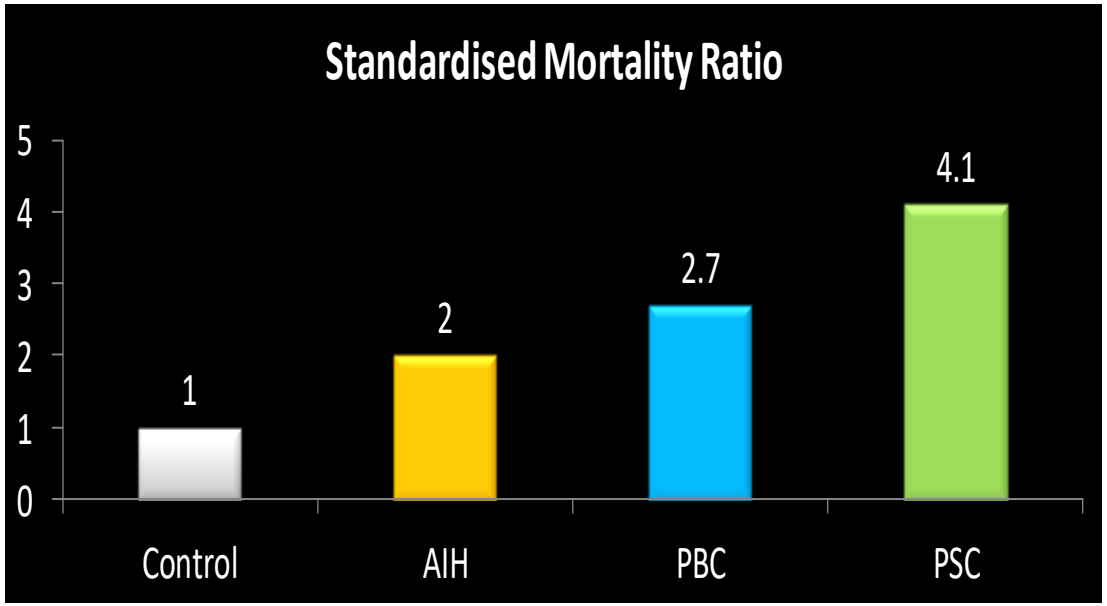
- ALT +/- AST elevation
  - ALT is higher in most causes of hepatocellular injury
  - If only AST raised consider non-liver causes
  - AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes
- AST:ALT ratio:
  - ALT normally higher than AST in acute hepatitis
  - Ratio >1 in alcoholic hepatitis, ischaemic hepatitis, cirrhosis

Common causes of hepatitis

- **Drugs**
  - Antibiotics, Augmentin, statin or herbal supplements
  - Amounts ingested, duration of use
- **Viral hepatitis**
  - Transfusion history, exposure to needles (Hep C)
  - Travelling history (Hep A and E)
  - Family history of viral hepatitis (Hep B)
- **Alcoholic hepatitis**
  - Amount, duration
  - Weekly recommended consumption limit (F=10 units, M=15 units)
- **Fatty liver (NAFLD)**
  - Metabolic history – diabetes, high cholesterol
- **Autoimmune hepatitis**

High Prevalence of Autoimmune Hepatitis in NZ





Ngu et al. J Gastroenterol Hepatol 2010
Ngu et al. Hepatology 2012

Tests to order – chronic hepatitis

- Viral hepatitis:
  - Hepatitis B surface antigen → HBV viral load
  - Hepatitis C antibody → HCV viral load
- Autoimmune hepatitis
  - Antinuclear antibodies, smooth muscle antibodies, immunoglobulin G
- *Ferritin (haemachromatosis), ceruloplasmin (Wilson's disease)*

Referral to tertiary centre

- Probable autoimmune hepatitis
  - Positive ANA, SMA or raised IgG – may need liver biopsy
- Hepatitis B with abnormal LFTs
  - Need fibroscan +/- treatment
- Worsening LFTs with synthetic dysfunction
  - Raised INR, raised bilirubin, low albumin
  - Developing liver failure
- Signs of cirrhosis or portal hypertension
  - Low platelet, splenomegaly
  - Ascites

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Patterns of Abnormal LFTs

- Hepatitic
  - Raised ALT, AST
- Cholestatic
  - Raised ALP, GGT

Common causes of cholestasis

- **Obstructive tumour e.g. pancreas**
- **Choledocholithiasis**
- Cholangiocarcinoma
- Drugs
- Autoimmune liver diseases
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis

Tests to order for cholestasis

- **Imaging : US abdomen**
- Autoimmune marker : Anti-mitochondrial antibodies (PBC)

Case

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Tests to order

- Viral hepatitis:
  - Hepatitis B surface antigen
  - Hepatitis C antibody
- Autoimmune markers
  - ANA, SMA, IgG
- US abdomen

Scenario 1

- Results:
  - ANA 1:320
  - IgG 25
  - Viral hepatitis serology negative
- Suspect autoimmune hepatitis

→ Refer to hospital for liver biopsy

Scenario 2

- Diabetes, hypertension, raised BMI
- Rest of tests negative
- US abdomen shows fatty liver

→ Probable NAFLD

2. Fatty Liver Epidemic

(Non-alcoholic Fatty Liver Disease)

Non-Alcoholic Fatty Liver Disease (NAFLD)

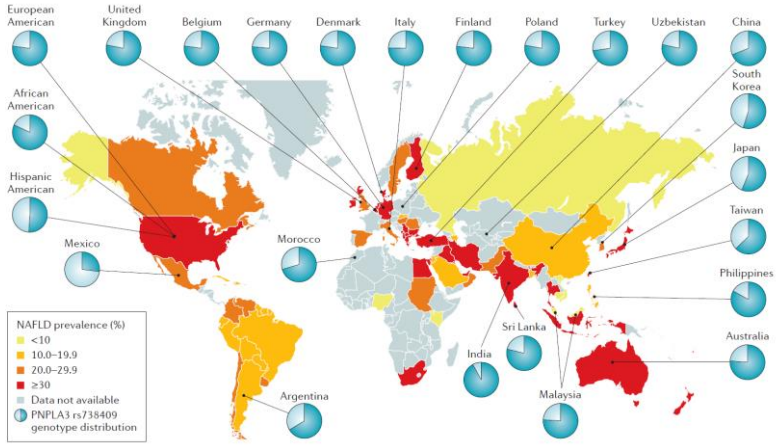
- Definition:
  - An accumulation of more than **5% fat within the liver** that is not attributable to alcohol or drugs

- NAFLD – includes two pathologically distinct conditions
  - 1) NAFL (non-alcoholic fatty liver) → simple steatosis without inflammation
  - 2) NASH (non-alcoholic steatohepatitis) → inflammatory cells infiltrate, injury and apoptosis of hepatocytes [inflammation → fibrosis→ cirrhosis → HCC]

Ngu et al. Singapore Med J 2016

How common is NAFLD?

- NAFLD is becoming the most common cause of liver disease
- NAFLD will likely be the leading cause of end-stage liver failure
- **Global prevalence is estimated to be 24%**
- More than 70% of Type II DM have NAFLD
- Incidence and prevalence of NAFLD is expected to increase rapidly with the obesity and diabetes mellitus epidemics



Younossi et al. Nat Rev Gastroenterol Hepatol. 2018
Ngu et al. Singapore Med J 2016

Natural history of NAFLD

- Considerable uncertainty about the natural history and prognosis of NAFLD
- Only a subset of NAFLD (10-25%) progress to serious complications such as cirrhosis, liver failure, HCC and death
- **The most important predictor of long term outcome in NAFLD is the presence or absence of advanced liver fibrosis**
- Average time needed to progress by one fibrosis stage:
  - NAFL – 14.3 years
  - NASH – 7.1 years

Angulo et al. Gastroenterol 2015
Satapathy et al. Semin Liver Dis 2015
Singh et al. Clin Gastroenterol Hepatol 2015

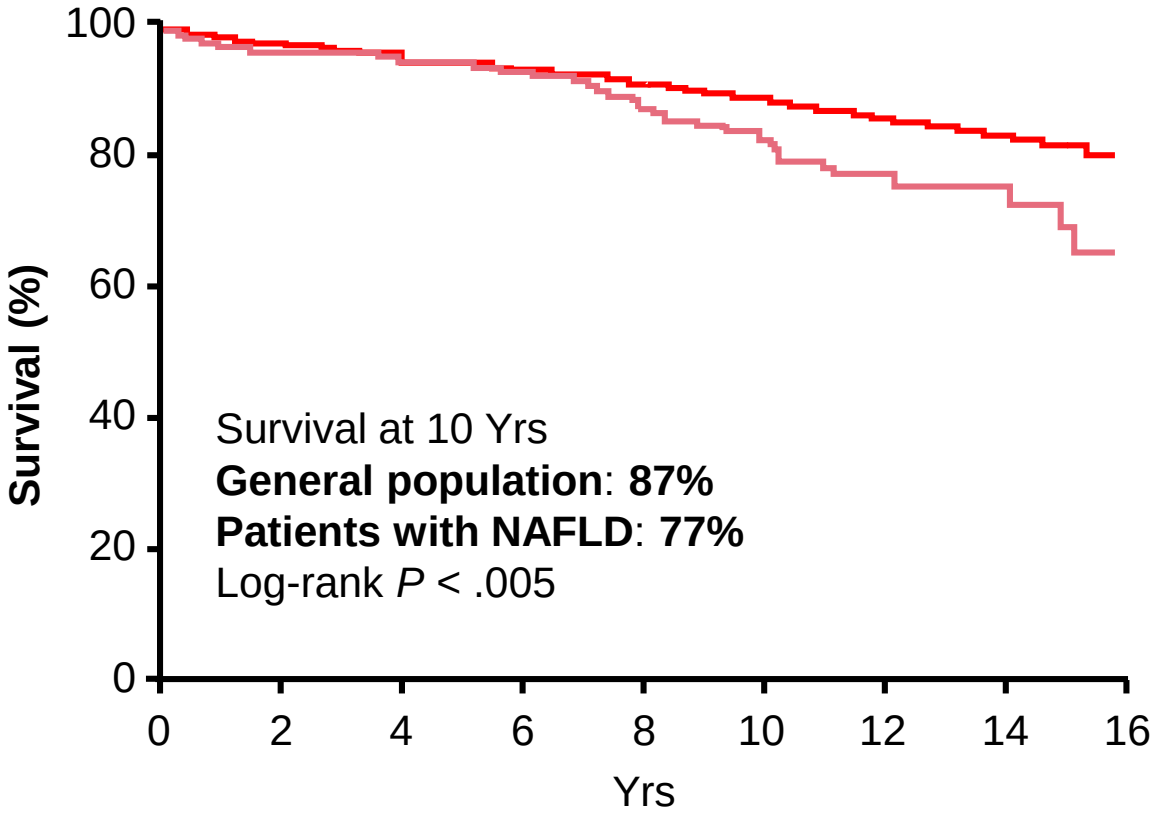
Gastroenterology 2015;149:389–397

Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

Paul Angulo,[1] David E. Kleiner,[2] Sanne Dam-Larsen,[3] Leon A. Adams,[4] Einar S. Bjornsson,[5] Phunchai Charatcharoenwitthaya,[6] Peter R. Mills,[7] Jill C. Keach,[8] Heather D. Lafferty,[7] Alisha Stahler,[8] Svanhildur Haflidadottir,[9] and Flemming Bendtsen[10]

Mortality in Patients With NAFLD

- Patients with NAFLD (N = 420) matched by age and sex to general population in Minnesota, followed for 7.6 ± 4.0 yrs



Top 3 Causes of Death in NAFLD, %	Patients (n = 53)
Malignancy	28
Heart disease	25
Liver disease	13

Gastroenterology. 2005;129:113-121.

How to diagnose NAFLD

- Diagnosis of NAFLD requires:
  - Presence of hepatic steatosis by imaging or histology
  - No significant alcohol consumption (>30g daily men, >20g daily women)
  - No competing aetiologies for hepatic steatosis
  - No co-existing causes for chronic liver disease

Chalasani et al. Hepatology 2012

Risk stratification in NAFLD

- Only a subset of NAFLD (10-25%) progress to serious complications such as cirrhosis, liver failure, HCC and death
- Fibrosis is the most important prognostic factor in NAFLD
- Stage of fibrosis correlated with liver-related outcomes and mortality

➔ Risk stratification by non-invasive fibrosis assessment

EASL–EASD–EASO Practice Guideline for the management of NAFLD 2016

Non-invasive assessment of fibrosis: Serum markers

- Serum markers (non-proprietary)
  - **FIB-4 (Fibrosis 4 score)**
- AUROC >0.8 in predicting advanced fibrosis
- Predict overall mortality, cardiovascular mortality and liver-related mortality
- Negative predictive value to exclude advanced fibrosis is high

EASL–EASD–EASO Practice Guideline for the management of NAFLD 2016

Fibrosis-4 (FIB-4) Calculator

Share

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age } (\textit{years}) \times \text{AST Level } (\textit{U/L})}{\text{Platelet Count } (\textit{10}^9/\textit{L}) \times \sqrt{\text{ALT } (\textit{U/L})}} =$$

Interpretation:

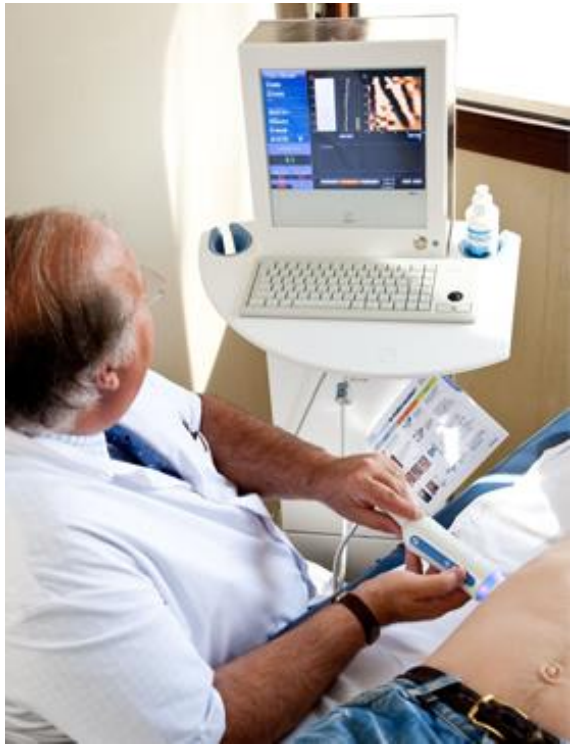
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Sources

Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.

Non-invasive assessment of fibrosis: Elastography

- Transient Elastography (Fibroscan)
  - Can be helpful in identifying advanced fibrosis or cirrhotic patients



Liver biopsy

- Confirm diagnosis – NASH
- Exclude other diagnosis – AIH (high IgG or positive autoantibodies)
- Staging - Presence of cirrhosis → HCC surveillance, variceal screening

  - Advanced fibrosis is a poor prognostic factor

Referral to tertiary centre

- Suspect concomitant liver disease
  - Positive ANA, SMA or raised IgG (autoimmune hepatitis)
  - Worsening LFTs
- Suspect advanced fibrosis
  - FIB-4 score > 1.45
- Signs of cirrhosis or portal hypertension
  - Low platelet, splenomegaly
  - Ascites

Management of NAFLD

- Uncomplicated NAFLD can be managed and followed up in the primary healthcare setting
- All NAFLD patients should undergo interventions aimed at promoting healthier lifestyle and strict control of metabolic risk factors
- Lifestyle modification is the first-line treatment for NAFLD patients

Treatment - Lifestyle modification

1. Weight loss:
   - Losing 3-5% of body weight improve steatosis
   - Losing 10% of body weight improve necroinflammation
2. Diet:
   - Low consumption of carbohydrate and saturated fat
   - Fructose riched diet is bad
   - Coffee is protective
3. Exercise:
   - 150 minutes of moderate to vigorous physical activities per week

Treatment – Metabolic risk factors

1. Diabetes mellitus – insulin sensitisers (metformin)
2. Dyslipidaemia – Statin
3. Hypertension – ACE inhibitor

Health Pathway Recommendation

- Calculate FIB-4 score:
  - If score < 1.45, significant liver fibrosis unlikely repeat in a year
  - If score > 1.45, refer for Fibroscan
- Provide advice on lifestyle modification
- Treat metabolic risk factors aggressively

Take home messages

- Prevalence of NAFLD is rapidly increasing
- NAFLD is not a benign condition
- Fibrosis scores can be used to identify NAFLD patients with advanced fibrosis
- Lifestyle modifications including weight loss, dietary changes and physical exercise are the mainstay of treatment
- Metabolic risk factors should be aggressively treated in NAFLD