Malaysian Society of Gastroenterology & Hepatology

Disclaimer statement

- The following slides are intended for educational purposes only and do not replace independent professional medical judgment
- Statements of facts and opinions expressed are those of the individual presenters and, unless expressly stated to the contrary, are not the opinion or position of the Malaysian Society of Gastroenterology and Hepatology (MSGH)
- Webinar-related materials are not to be used for the promotion of commercial products
- All webinar materials are the sole property of the MSGH and cannot be published, copied, or disseminated without prior approval
- Please acknowledge "Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD): A New Name For An Old Foe http://msgh.org.my" if the slides are shared for educational purposes

37 year old with elevated liver enzymes

Case Presentation 2

Dr Ng Inn Shan
Clinical Specialist in Hepatology
Department of Hepatology
Hospital Selayang

Outline

- Case introduction
- History and examination
- Blood investigations
- Approach to the case
- Discussion

Presenting history

- Mr A, 37 years old gentleman
- Under Surgical Department follow up for GERD with hiatal hernia
- Routine blood investigation noted **elevated liver enzymes**

Liver Profile	17/10/2017
Total bilirubin	33
ALT	87
AST	46
ALP	92
Albumin	41

- USG HBS done shows **fatty liver**

First review in Hepatology clinic

- Premorbid history
  - Well controlled **bronchial asthma**
  - **GERD with hiatal hernia** under SOPD follow up

- Asymptomatic, feels well
- Does not smoke or drink alcohol
- No high risk behaviour
- Denies parental consanguinity
- Denies family history of chronic liver disease

Medication review

- MDI salbutamol PRN basis – rarely
- Tab pantoprazole 40mg OD

- Does not take steroid
- Denies herbal supplements, direct sales products or OTC medications

Examination findings

- Obese
- Blood pressure 120/80mmHg
- Body weight of **88kg** at presentation with **BMI 28.08**
- No stigmata of chronic liver disease

Baseline investigations

FBC	30/10/2017
TWC	8.43
Hb	16.6
HCT	46
Platelet	262

Renal profile	30/10/2017
Urea	2.9
Creatinine	84

Infective screen	30/10/2017
HBsAg	NR
Anti HCV	NR

LFT	30/10/2017
Total bilirubin	33
Albumin	43
ALP	103
ALT	87
AST	40

FLP & FBS	30/10/2017
Total Cholesterol	4.4
Triglyceride	2.3
HDL-C	1.0
LDL-C	2.4
FBS	6.3

- What is your comment on the blood investigations?
- What are the additional investigations that you want to order

Do we have enough information to diagnose MALFD?

Yes or No?

Algorithm to diagnose and manage MALFD

Hepatology International
https://doi.org/10.1007/s12072-020-10094-2

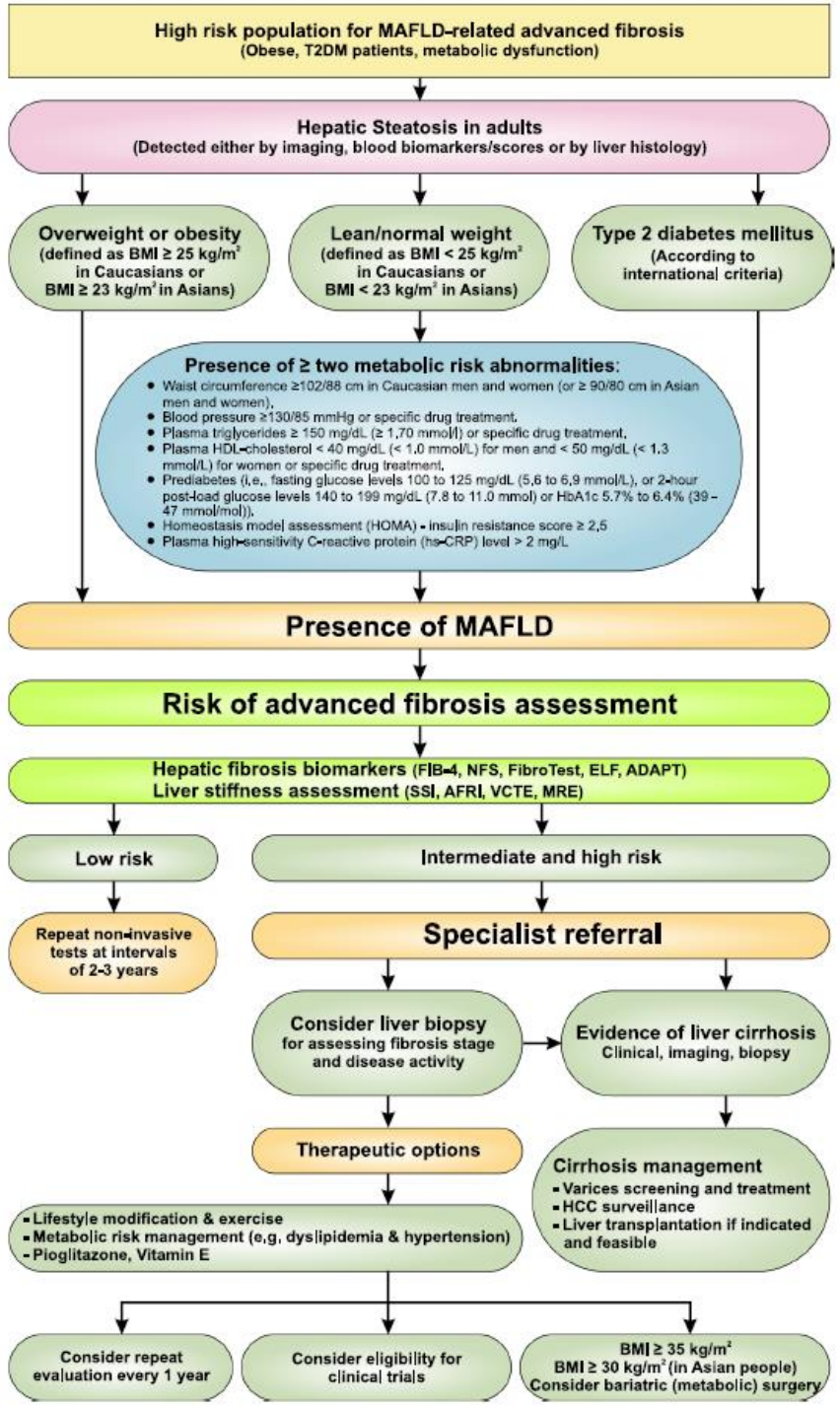
GUIDELINES

Check for updates

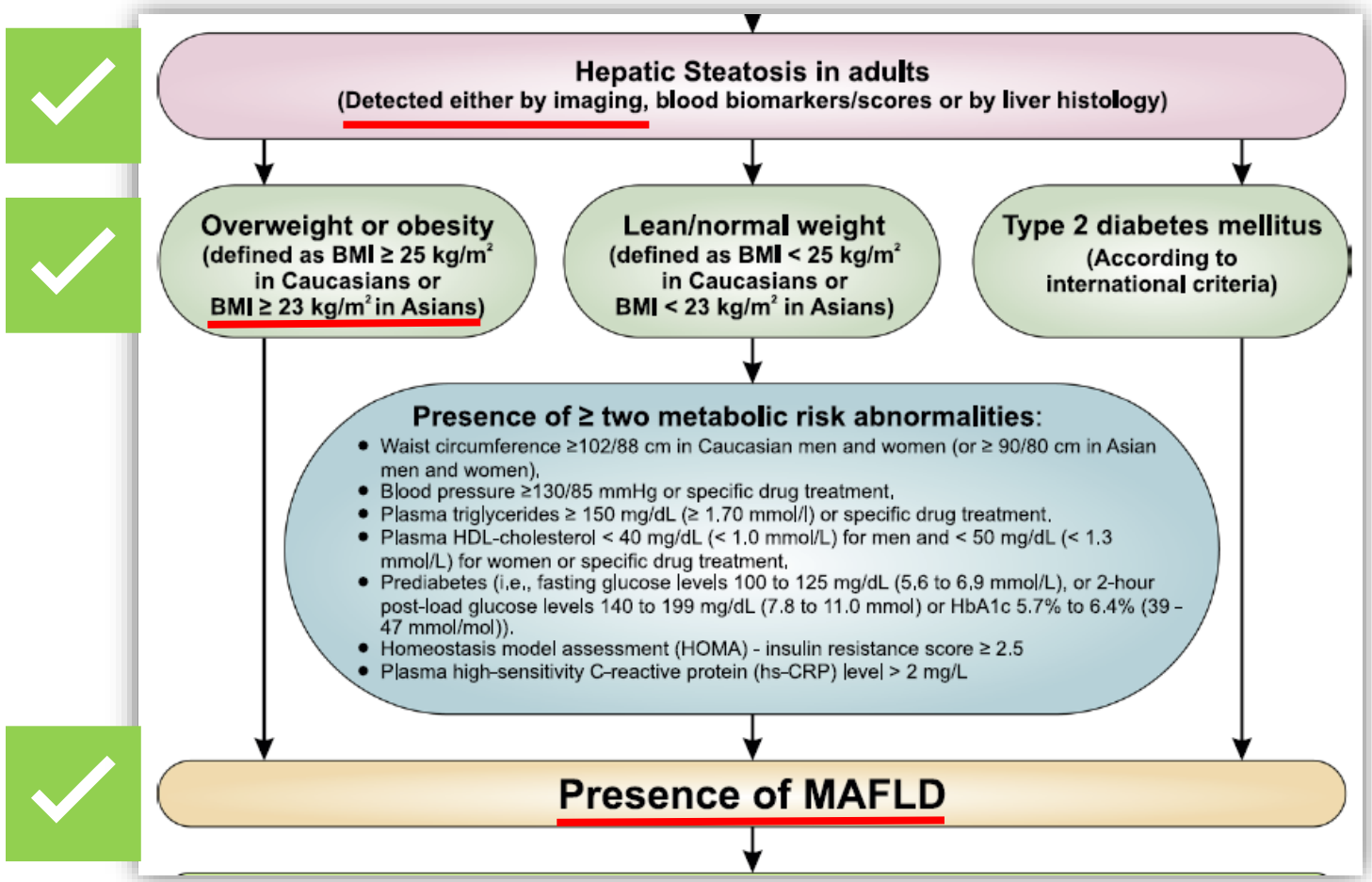
The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease

Mohammed Eslam[1] · Shiv K. Sarin[2] · Vincent Wai-Sun Wong[3] · Jian-Gao Fan[4] · Takumi Kawaguchi[5] · Sang Hoon Ahn[6] · Ming-Hua Zheng[7,8] · Gamal Shiha[9,10] · Yusuf Yilmaz[11,12] · Rino Gani[13] · Shahinul Alam[14] · Yock Young Dan[15] · Jia-Horng Kao[16,17,18,19] · Saeed Hamid[20] · Ian Homer Cua[21] · Wah-Kheong Chan[22] · Diana Payawal[23] · Soek-Siam Tan[24] · Tawesak Tanwandee[25] · Leon A. Adams[26] · Manoj Kumar[2] · Masao Omata[27,28] · Jacob George[1]

Received: 8 July 2020 / Accepted: 6 September 2020


High risk population for MAFLD-related advanced fibrosis
(Obese, T2DM patients, metabolic dysfunction)
Hepatic Steatosis in adults
(Detected either by imaging, blood biomarkers/scores or by liver histology)
Overweight or obesity
(defined as BMI ≥ 25 kg/m² in Caucasians or BMI ≥ 23 kg/m² in Asians)
Lean/normal weight
(defined as BMI < 25 kg/m² in Caucasians or BMI < 23 kg/m² in Asians)
Type 2 diabetes mellitus
(According to international criteria)
Presence of ≥ two metabolic risk abnormalities:
Waist circumference ≥102/88 cm in Caucasian men and women (or ≥ 90/80 cm in Asian men and women).
Blood pressure ≥130/85 mmHg or specific drug treatment.
Plasma triglycerides ≥ 150 mg/dL (≥ 1,70 mmol/l) or specific drug treatment.
Plasma HDL-cholesterol < 40 mg/dL (< 1,0 mmol/L) for men and < 50 mg/dL (< 1,3 mmol/L) for women or specific drug treatment.
Prediabetes (i.e,. fasting glucose levels 100 to 125 mg/dL (5,6 to 6,9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39 – 47 mmol/mol)).
Homeostasis model assessment (HOMA) - insulin resistance score ≥ 2,5
Plasma high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L
Presence of MAFLD
Risk of advanced fibrosis assessment
Hepatic fibrosis biomarkers (FIB-4, NFS, FibroTest, ELF, ADAPT)
Liver stiffness assessment (SSI, AFRI, VCTE, MRE)
Low risk
Intermediate and high risk
Repeat non-invasive tests at intervals of 2-3 years
Specialist referral
Consider liver biopsy
for assessing fibrosis stage and disease activity
Evidence of liver cirrhosis
Clinical, imaging, biopsy
Therapeutic options
Cirrhosis management
- Varices screening and treatment
- HCC surveillance
- Liver transplantation if indicated and feasible
- Lifestyle modification & exercise
- Metabolic risk management (e,g, dyslipidemia & hypertension)
- Pioglitazone, Vitamin E
Consider repeat evaluation every 1 year
Consider eligibility for clinical trials
BMI ≥ 35 kg/m²
BMI ≥ 30 kg/m² (in Asian people)
Consider bariatric (metabolic) surgery

Diagnosis of MAFLD



Hepatic steatosis

- Imaging – **USG**, CAP, MRS, MRI-PDFF
- Blood biomarkers – Fatty liver index (FLI)
- Liver histology – steatosis in >5% hepatocytes

Common question:
Limited setting without assess to ultrasound especially in primary care, what are the alternative?

Fatty liver index

Validation of the Fatty Liver Index for Nonalcoholic Fatty Liver Disease in Middle-Aged and Elderly Chinese

Xiaolin Huang, MD, Min Xu, PhD, Ying Chen, MD, Kui Peng, MD, Ya Huang, MD, Po Wang, MD, Lin Ding, MD, Lin Lin, MD, Yu Xu, PhD, Yuhong Chen, MD, PhD, Jieli Lu, MD, PhD, Weiqing Wang, MD, PhD, Yufang Bi, MD, PhD, and Guang Ning, MD, PhD

Monitoring Editor: Farid Azmoudeh-Ardalan.

Abstract

Go to:

The fatty liver index (FLI), which is an algorithm based on waist circumference, body mass index (BMI), triglyceride, and gamma-glutamyl-transferase (GGT), was initially developed to detect fatty liver in Western countries. Our study aimed to evaluate the accuracy and optimal cut-off point of the FLI for predicting nonalcoholic fatty liver disease (NAFLD) in middle-aged and elderly Chinese.

This cross-sectional study included 8626 Chinese adults aged 40 years or above recruited from Jiading District, Shanghai, China. Anthropometric and biochemical features were collected by a standard protocol. NAFLD was diagnosed by hepatic ultrasonography. The accuracy and cut-off point of the FLI to detect NAFLD were evaluated by area under the receiver operator characteristic curve (AUROC) and the maximum Youden index analysis, respectively.

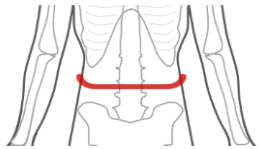
The AUROC of the FLI for NAFLD was 0.834 (95% confidence interval: 0.825–0.842), and larger than that of its each individual component [0.786 (0.776–0.796), 0.783 (0.773–0.793), 0.727 (0.716–0.739), and 0.707 (0.695–0.719) for waist circumference, BMI, triglyceride, and GGT, respectively] (all $P<0.001$). The optimal cut-off point of the FLI for diagnosing NAFLD was 30 with the maximum Youden Index of 0.51, achieving a high sensitivity of 79.89% and a specificity of 71.51%. The FLI-diagnosed NAFLD individuals were in worse metabolic characteristics (waist circumference, BMI, blood pressure, serum lipids, and aminotransferases) than ultrasonography-diagnosed NAFLD patients (all $P<0.05$).

The FLI could accurately identify NAFLD and the optimal cut-off point was 30 in middle-aged and elderly Chinese. As FLI-diagnosed NAFLD patients were in worse metabolism, much attention should be paid to the metabolic controls and managements of NAFLD.

Parameters:

Waist circumference, Triglyceride, GGT, BMI

FLI is simple to obtain and may help physicians select subjects for liver ultrasonography



- **Waist circumference** and **BMI** were the strongest predictors of FL
- Among liver enzymes, only **GGT** was an independent predictor of FL
- **Triglycerides** were independent predictors of FL

- **FLI < 30** ruled out and a **FLI ≥ 60** ruled in hepatic steatosis

Bedogni, Giorgio et al. "The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population." BMC gastroenterology vol. 6 33. 2 Nov. 2006, doi:10.1186/1471-230X-6-33

We have the diagnosis of MAFLD, but what is next?

Are we done at this point?

Issues with Mr. A

- **Elevated liver enzymes** (Any possibilities of coexisting liver condition other than MAFLD?)
- **Impaired fasting glucose** at presentation,
- **Obesity**
- **Fibrosis score?**

- Why hyperbilirubinemia?
  - Not related to MALFD – possible Gilbert syndrome
  - However no direct/indirect bilirubin level taken

Fatty Liver with elevated liver enzymes

- MAFLD
- Alcohol related fatty liver disease
- Steatogenic medications – steroid, valproic acid, tamoxifen, MTX, amiodarone...etc
- HCV genotype 3 infection
- Wilson disease
- Coeliac disease
- Lipid metabolism disorder
- Familial combined hyperlipidemia
- Etc...

Would you decide for **liver biopsy** at this point?

Impaired fasting glucose

- Mr. A has fasting blood sugar of **6.3**, but asymptomatic

CPG Management of T2DM (6th Edition)

Figure 2-2: Screening for T2DM in asymptomatic individuals

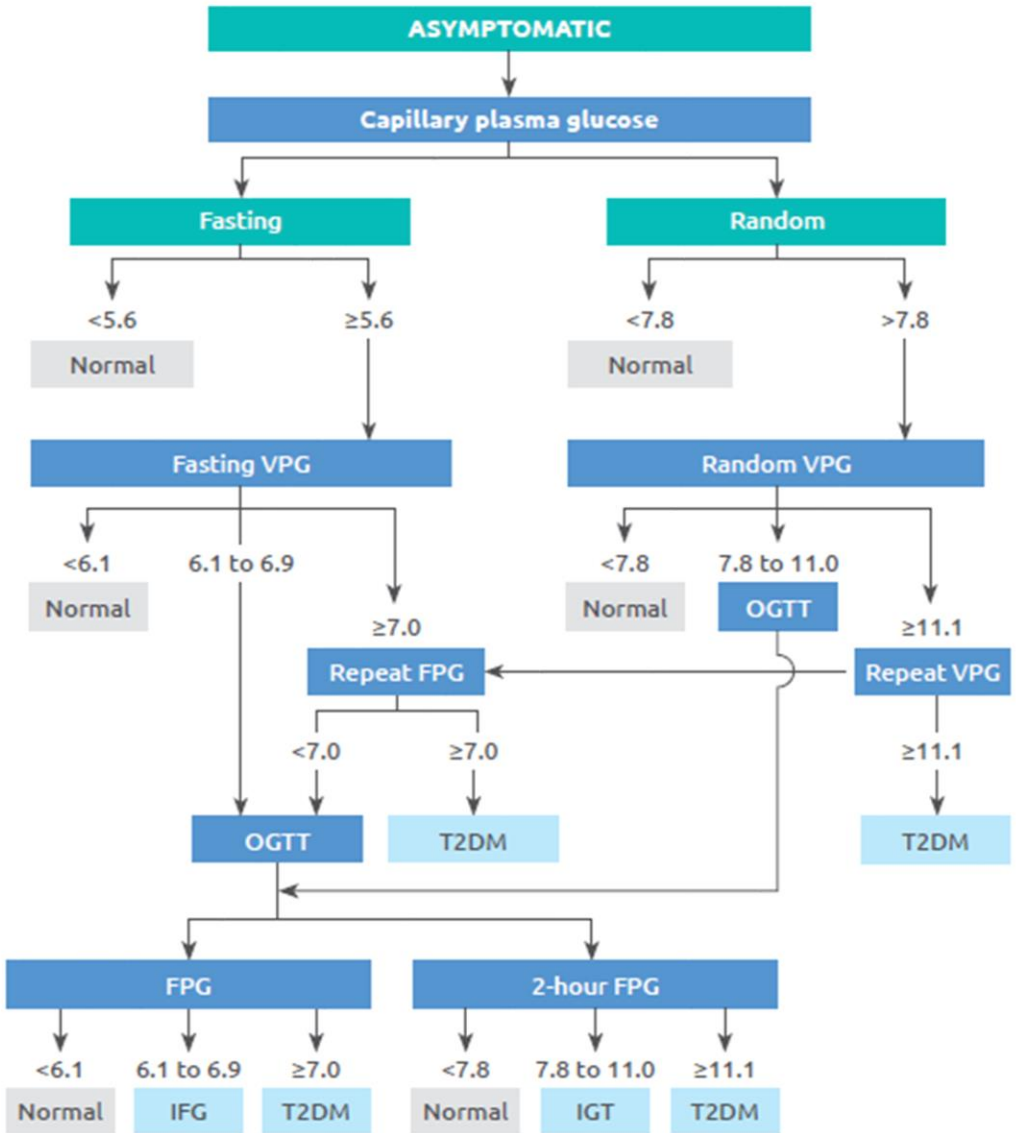
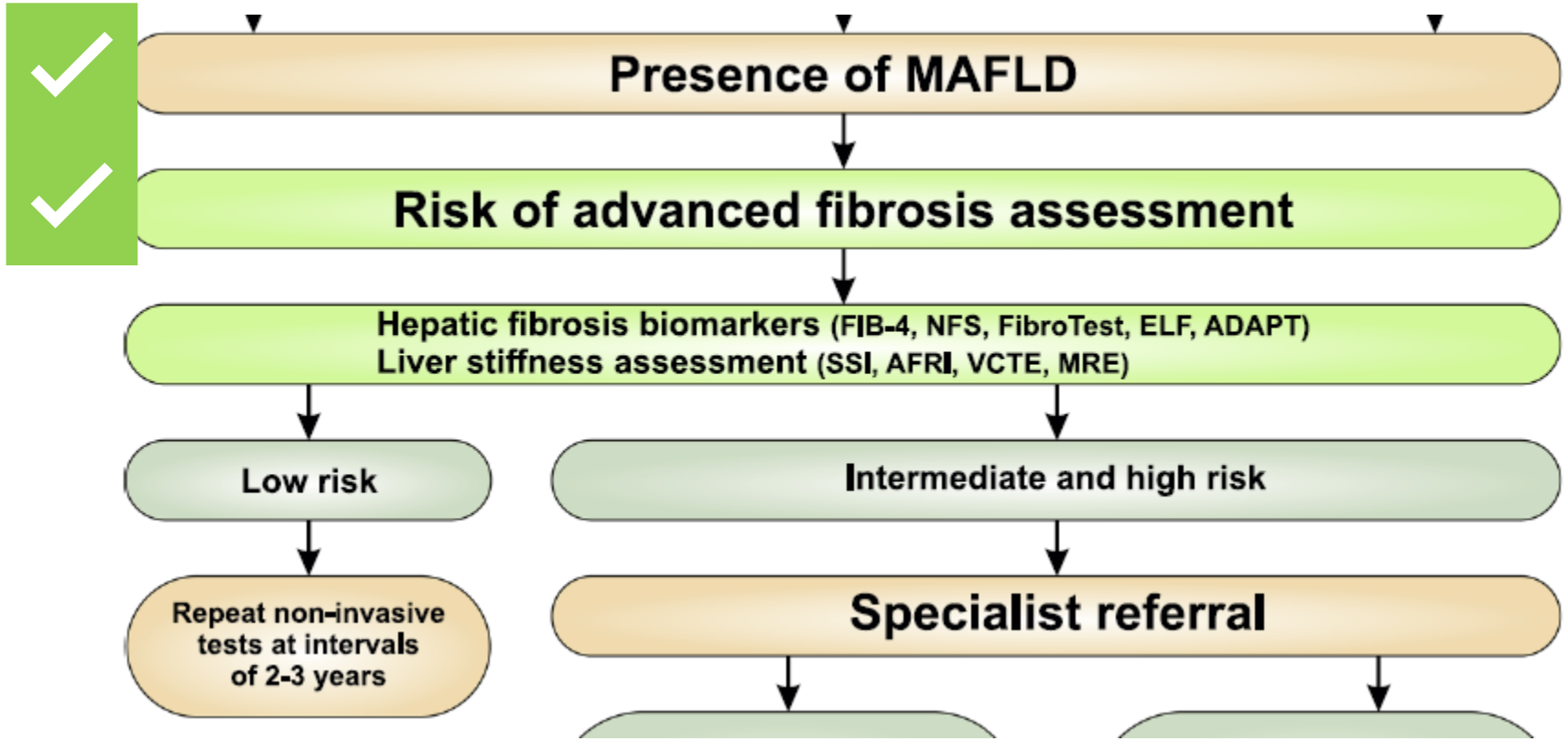


Table 2-5: Diagnostic value for prediabetes and T2DM based on HbA_{1c}

	Normal	Prediabetes	T2DM
HbA_{1c}	<5.7% (<39 mmol/mol)	5.7%-<6.3% (39-44 mmol/mol)	≥6.3% (≥45 mmol/mol)

A repeat HbA_{1c} should be done 4 weeks after the first positive test for asymptomatic patients (if an accompanying FPG or RPG is indeterminate). For symptomatic patients, a single positive test is sufficient.
FPG: fasting plasma glucose; RPG: random plasma glucose

Simple fibrosis score



FIB-4 score

When is **Fibroscan** indicated?
Is it indicated in this case?

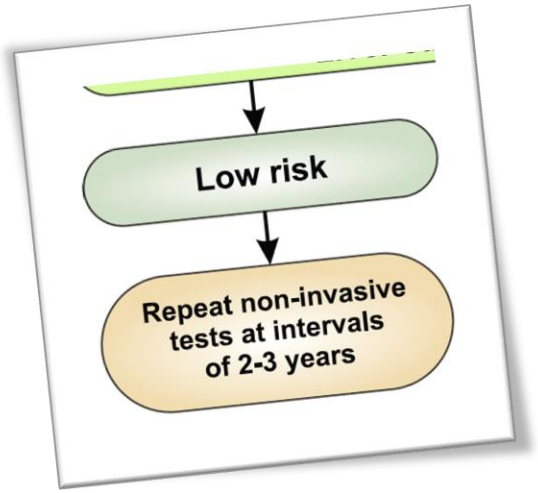
- Fib-4 score < 1.3 – **low risk**
- Fib-4 score > 1.3 – **intermediate to high risk**

- Mr. A score calculated;

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} = 0.61$$

Age (years): 37 × AST Level (U/L): 40 / Platelet Count (10^9/L): 262 × √ALT (U/L): 87 = 0.61

Strong negative predictive value
– advance fibrosis ruled out
= LOW RISK case



CV Risk assessment

- Framingham CVD Risk score MD+CALC
- Assess CVD risk and need for statin

Table 5: Target LDL-C Levels

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C Levels (mmol/L)	Non HDL-C Level corresponding to LDL-C targets in individuals with TG > 4.5 mmol/L
Low CV Risk*	clinical judgement**	< 3.0	< 3.8
Intermediate (Moderate) CV Risk*	> 3.4 **	< 3.0	< 3.8
High CV risk >20% 10-year CVD risk diabetes without target organ damage CKD with GFR 30-<60 Ml/ $min^{-1}/1.73m^2$	> 2.6	**≤ 2.6 or a reduction of > 50% from baseline*** **	**≤ 3.4 or a reduction of > 50% from baseline*** **
Very high CV risk established CVD, diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia CKD with GFR <30 Ml/ $min^{-1}/1.73m^2$ but not dialysis dependent)****	> 1.8	**< 1.8 or a reduction of > 50% from baseline*** **	**< 2.6 or a reduction of > 50% from baseline*** **

**Low and Intermediate (Moderate) CV risk is assessed using the Framingham General CVD Risk Score*
***After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient*
****whichever results in a lower level of LDL-C*
*****In dialysis dependent patients,drug therapy is not indicated for primary prevention of CVD.*

- Using Framingham CVD risk score
- Mr. A has 0.5% 10-year risk for CVD (**LOW RISK**); statin is not required

- However, **target LDL-C < 3.0** in low risk patient – can consider initiation of statin based on judgement

CPG Dyslipidemia 2017

Follow up plan for Mr. A

1. Weight loss

Weight loss	Outcome
> 5%	Improvement in liver histology in 58%
> 10%	Improvement in liver histology in 90% and improvement in fibrosis stage

- Aim gradual weight loss up to 1kg/week

2. Refer dietitian for low caloric diet
3. Moderate intensity exercise (150minutes/week) vs Resistance exercise (2-3 days/week)

Follow up plan for Mr. A

4. Refer to primary care physician for management of associated metabolic disorders
5. Screening for secondary causes such as Wilson disease
   - Serum ceruloplasmin, urine copper, refer Ophthal for slit lamp examination for KF ring

Mr. A subsequent visits

Summary of encounters

Reviews

- Mr. A did not lose significant weight
- Remains sedentary
- Defaulted dietitian review
- No KF rings. Serum ceruloplasmin normal.

Blood parameters					
Total bilirubin	33	44	28		41
AST	40	41	20		28
ALT	87	77	35		53
Platelets	262	288	286		270
FBS	6.3		5.8		6.6
HbA1C					6.5
Triglyceride	2.3		1.9		1.9
LDL- C	2.4		3.0		3.2
HDL-C	1.0		1.2		1.2
FIB-4 score	0.61				0.58
Body weight	88.0		**87.5**		
BMI	28.08		27.9		

M

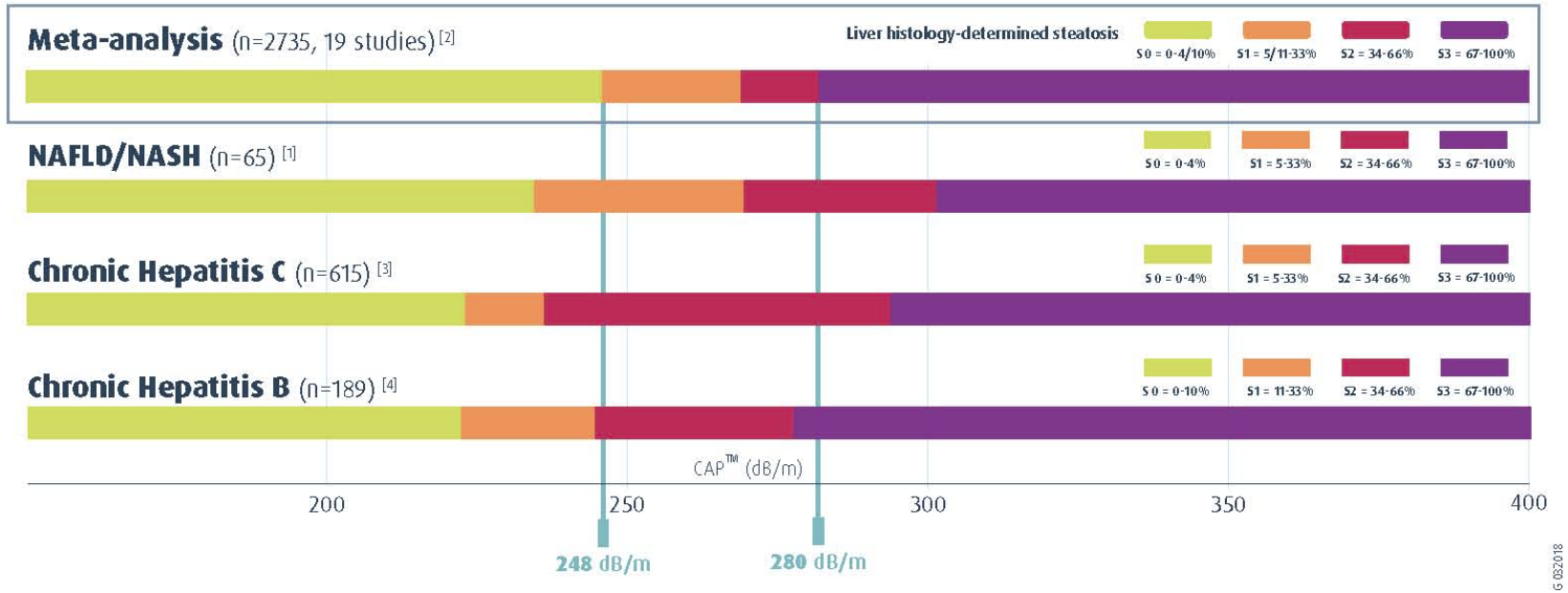
C

O

[--- VIRTUAL CLINIC ---]

Discussion

- Patient did progress from IFG to T2DM during subsequent follow up
- A Fibroscan was ordered – Liver stiffness 3.9kPa, CAP 282



Summary

- MAFLD without advance fibrosis is common in primary care setting
- MAFLD is a multi-system disease; holistic approach is needed
- Adequate counselling is required to emphasis on the importance of lifestyle modification

Thank you for your attention