Screening cardiac patients for advanced liver disease

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Pamela Youde Nethersole Eastern Hospital
NAFLD is common

- A common chronic liver disease worldwide
  - 10-33% population worldwide
  - 27.3% population prevalence in HK (by proton-magnetic resonance spectroscopy)
- NAFLD is even more common amongst CAD (coronary artery disease) patients
  - 58.2% amongst 612 patients with coro +/- PCI in a CUHK study (Gut 2011;60:1721-27)
  - Similar findings in many Caucasian studies
Natural Course

- NAFLD
- NASH
- NASH cirrhosis
- HCC

General population:
- 20% for BMI > 40
- 90% for BMI ≥ 40
- 3-5% for BMI < 40

Annual incidence:
- 2-3%?
- 5%?
Why bother about advanced fibrosis in NAFLD?

Fibrosis Stage Is the Strongest Predictor for Disease-Specific Mortality in NAFLD After Up to 33 Years of Follow-Up

Mattias Ekstedt,1* Hannes Hagström,2* Patrik Nasr,3 Mats Fredrikson,3 Per Stål,2 Stergios Kechagias,3 and Rolf Hultcrantz2

Hepatology 2015;61:1547-54.
Why bother about advanced fibrosis in NAFLD?

- Worse prognosis in NAFLD patients with advanced fibrosis
  - Higher *overall* mortality, irrespective of underlying NASH activity, c/w those with mild fibrosis
  - Highest *liver*-related mortality amongst NAFLD patients (portal HT, liver failure & HCC)

_Hepatology* 2015;61:1547-54.
Why bother about advanced fibrosis in NAFLD?

• Management
  – Reduction of body mass index & waist circumference is associated with static or improved fibrosis stage on histology
  – Consideration of OV and HCC screening
  – Novel therapeutic agents are in development and are expected to offer unique options to NASH patients with advanced fibrosis
Transient elastography in diagnosis of advanced liver fibrosis

- High sensitivity & specificity to identify advanced fibrosis & cirrhosis in NAFLD
  - ROC curves in detecting advanced fibrosis & cirrhosis: 0.93 & 0.95 respectively

<table>
<thead>
<tr>
<th>Stage</th>
<th>AUROC</th>
<th>Cutoff (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥F2</td>
<td>0.84 (0.79-0.90)</td>
<td>5.8</td>
<td>91.1</td>
<td>50.3</td>
<td>56.1</td>
<td>89.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.0</td>
<td>79.2</td>
<td>75.9</td>
<td>69.6</td>
<td>84.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.0</td>
<td>52.5</td>
<td>91.7</td>
<td>81.5</td>
<td>73.5</td>
</tr>
<tr>
<td>≥F3</td>
<td>0.93 (0.89-0.96)</td>
<td>7.9</td>
<td>91.1</td>
<td>75.3</td>
<td>52.0</td>
<td>96.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7</td>
<td>83.9</td>
<td>83.2</td>
<td>59.5</td>
<td>94.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.6</td>
<td>75.0</td>
<td>91.6</td>
<td>72.4</td>
<td>92.6</td>
</tr>
<tr>
<td>F4</td>
<td>0.95 (0.91-0.99)</td>
<td>10.3</td>
<td>92.0</td>
<td>87.8</td>
<td>46.0</td>
<td>99.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.3</td>
<td>92.0</td>
<td>87.8</td>
<td>46.0</td>
<td>99.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.5</td>
<td>76.0</td>
<td>91.0</td>
<td>48.7</td>
<td>97.1</td>
</tr>
</tbody>
</table>

NAFLD with advanced fibrosis is uncommon in general population

- Advanced fibrosis is only present in 3.7% of NAFLD patients in the general HK Chinese population

*Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography*

Vincent Wai-Sun Wong,¹,² Winnie Chiu-Wing Chu,¹,³ Grace Lai-Hung Wong,¹,² Ruth Suk-Mei Chan,⁴ Angel Mei-Ling Chim,¹,² Arlinking Ong,¹,²,⁵ David Ka-Wai Yeung,⁶ Karen Kar-Lum Yiu,¹,² Shirley Ho-Ting Chu,¹,² Jean Woo,²,⁴ Francis Ka-Leung Chan,¹,² Henry Lik-Yuen Chan¹,²

How about amongst CAD patients?

- Little data on the prevalence of advanced fibrosis in NAFLD patients with CAD, both locally and in the literature.
Non-alcoholic fatty liver disease and advanced fibrosis by transient elastography in Hong Kong Chinese patients with angiographically proven coronary artery disease

NAFLD AND ADVANCED FIBROSIS BY TRANSIENT ELASTOGRAPHY IN HONG KONG CHINESE PATIENTS WITH ANGIOGRAPHICALLY PROVEN CAD
Objectives

• Determine the prevalence of advanced fibrosis by transient elastography in NAFLD patients with angiographically proven CAD

• Examine the role of NAFLD as an independent predictive factor of significant CAD
Methods
Subjects & study design

• Cross-sectional study
  – Over a 9-month period from 10 Feb 2014 to 10 Nov 2014

• Inclusion criteria
  – All adult Chinese patients (≥ age 18) who underwent elective or emergency coronary angiogram for evaluation of suspected CAD at Pamela Youde Nethersole Eastern Hospital
Methods
Subjects & study design

- Exclusion criteria
  - Alcoholism (M ≥140g/wk, F ≥70g/wk)
  - On medications which could cause secondary hepatic steatosis (e.g. methotrexate, tamoxifen)
  - HBsAg +ve, anti-HCV +ve or ANA >1:160
  - Contraindications to transient elastography
    - PCM/ICD in-situ, ascites/CAPD
  - Conditions which can cause falsely ↑LSM
    - ALT >5*ULN, biliary obstruction, moderate to severe TR, features of hepatic congestion on USG
Methods
Patient workup

• Admission to medical day ward for workup within 2 weeks from the date of coro±PCI
• Anthropometric parameters
  – BMI, weight, height, waist/hip circumference
• Blood pressure
• Ultrasonography of abdomen
• Transient elastography
• Blood taking
Methods
Patient workup

• Diagnosis of NAFLD with advanced fibrosis by transient elastography (ALL 4 criteria)
  – Fatty liver diagnosed on USG
  – Valid LSM $\geq 9.6\text{kPa}$ on transient elastography
  – No evidence of hepatic congestion on USG
  – Exclusion of alcoholic, viral, autoimmune and metabolic causes of chronic liver diseases
Methods

Patient workup

• Coronary angiogram
  – *Significant CAD*: ≥70% of stenosis in one or more major coronary arteries (or ≥50% of the left main stem)
  – *Significant multi-vessel CAD*: 2 or more major coronary arteries having ≥70% stenosis
526 patients underwent coronary angiogram for ACS/stable angina/CAD on non-invasive tests

Exclusion
6 were of ethnicity other than Chinese
140 refused/unable to consent
37 had excessive alcohol consumption
19 had hepatitis B infection
2 had hepatitis C infection
4 had ANA titer >1:160
5 were on methotrexate
2 were on tamoxifen
14 were on continuous ambulatory peritoneal dialysis
11 had pacemaker or ICD in-situ
3 had ALT >5*upper limit of normal
18 had moderate to severe tricuspid regurgitation
15 had normal coronary angiogram

250 patients recruited into the study and received workup

Exclusion
5 found to have hepatitis B infection
1 found to have hepatitis C infection
3 found to have ANA>1:160
5 had evidence of hepatic congestion on USG

236 patients included into the final analysis
236 patients included into the final analysis

137 had NAFLD on USG
- 127 had valid LSM by transient elastography
  - 17 had advanced liver fibrosis (LSM ≥9.6 kPa)

99 did not have NAFLD on USG
- 93 had valid LSM by transient elastography
  - 4 had advanced liver fibrosis (LSM ≥9.6 kPa)

58.1%

13.4%
Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>NAFLD</th>
<th>No NAFLD</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>236</td>
<td>137</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (56-74)</td>
<td>63 (55-70)</td>
<td>69 (61-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>172 (72.9)</td>
<td>100 (73.0)</td>
<td>72 (72.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0 (23.2-28.2)</td>
<td>26.3 (23.9-29.3)</td>
<td>23.7 (22.0-26.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overweight/obese, n (%)</td>
<td>185 (78.4)</td>
<td>120 (87.6)</td>
<td>65 (65.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91.8 (86.0-97.0)</td>
<td>95.0 (89.5-101.3)</td>
<td>89.0 (82.0-94.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal obesity, n (%)</td>
<td>162 (68.6)</td>
<td>113 (82.5)</td>
<td>49 (49.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>97.0 (92.0-102.0)</td>
<td>98.0 (94.0-104.0)</td>
<td>94.0 (89.5-98.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.94 (0.91-0.99)</td>
<td>0.96 (0.91-1.00)</td>
<td>0.93 (0.90-0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>76 (32.2)</td>
<td>44 (32.1)</td>
<td>32 (32.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Current drinker, n (%)</td>
<td>35 (14.8)</td>
<td>21 (15.3)</td>
<td>14 (14.1)</td>
<td>0.80</td>
</tr>
</tbody>
</table>
Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>NAFLD</th>
<th>No NAFLD</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>172 (72.9%)</td>
<td>100 (73.0%)</td>
<td>72 (72.7%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 (116-145)</td>
<td>129 (114-141)</td>
<td>133 (116-147)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>68 (61-76)</td>
<td>70 (62-76)</td>
<td>65 (60-75)</td>
<td>0.075</td>
</tr>
<tr>
<td>IFG/diabetes mellitus</td>
<td>138 (58.5%)</td>
<td>90 (65.7%)</td>
<td>48 (48.5%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.5 (4.9-6.7)</td>
<td>5.7 (5.0-6.7)</td>
<td>5.2 (4.9-6.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>Haemoglobin A1c (%)</td>
<td>6.1 (5.8-6.8)</td>
<td>6.2 (5.9-6.8)</td>
<td>6.0 (5.8-6.7)</td>
<td>0.062</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.1 (3.7-4.5)</td>
<td>4.1 (3.6-4.5)</td>
<td>4.2 (3.7-4.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.3 (1.9-2.7)</td>
<td>2.2 (1.9-2.7)</td>
<td>2.3 (1.9-2.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>146 (61.9%)</td>
<td>106 (77.4%)</td>
<td>40 (40.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.1 (0.9-1.3)</td>
<td>1.0 (0.9-1.2)</td>
<td>1.2 (1.1-1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>129 (54.7%)</td>
<td>93 (67.9%)</td>
<td>36 (36.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.2 (0.9-1.8)</td>
<td>1.4 (1.0-1.9)</td>
<td>1.1 (0.8-1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>172 (72.9%)</td>
<td>122 (89.1%)</td>
<td>50 (50.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>12 (9-14)</td>
<td>12 (9-15)</td>
<td>11 (9-14)</td>
<td>0.42</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>73 (60-91)</td>
<td>72 (60-87)</td>
<td>76 (59-93)</td>
<td>0.41</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>21 (15-29)</td>
<td>24 (17-31)</td>
<td>18 (13-24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT elevated, n (%)</td>
<td>65 (27.5%)</td>
<td>50 (36.5%)</td>
<td>15 (15.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>21 (18-25)</td>
<td>21 (18-26)</td>
<td>20 (17-24)</td>
<td>0.066</td>
</tr>
</tbody>
</table>
Key findings 1

- All the components of metabolic syndrome independently predicted NAFLD, except for HT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity $^\text{Q}$</td>
<td>4.09 (1.66-10.07)</td>
<td>0.002</td>
</tr>
<tr>
<td>IFG/diabetes mellitus $^\text{Q}$</td>
<td>2.39 (1.04-5.51)</td>
<td>0.041</td>
</tr>
<tr>
<td>Low HDL-cholesterol $^\text{Q}$</td>
<td>4.42 (2.09-9.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertriglyceridemia $^\text{Q}$</td>
<td>2.69 (1.32-5.49)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

$^\text{Q}$ Covariates included age, body mass index, abdominal obesity $^\text{Q}$, systolic BP, diastolic BP, IFG/diabetes mellitus $^\text{Q}$, fasting glucose, haemoglobin A1c, low HDL-cholesterol $^\text{Q}$, hypertriglyceridemia $^\text{Q}$, ALT and AST (Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 6.503$, df=8, p=0.591).

$^\text{Q}$ Defined according to the metabolic syndrome criteria by International Diabetes Federation in 2009, with ethnicity-specific criteria for abdominal obesity in Asians.

NAFLD, non-alcoholic fatty liver disease; IFG, impaired fasting glucose; HDL, high-density lipoprotein; BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
### Table 3: Valid liver stiffness measurements in patients with and without NAFLD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>NAFLD</th>
<th>No NAFLD</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>220</td>
<td>127</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Valid LSM (kPa)</td>
<td>5.6 (4.4-7.1)</td>
<td>6.1 (4.9-7.6)</td>
<td>4.9 (4.2-6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valid LSM ≥9.6 kPa, n (%)</td>
<td>21 (9.5)</td>
<td>17 (13.4)</td>
<td>4 (4.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>Valid LSM &lt;9.6 kPa, n (%)</td>
<td>199 (90.5)</td>
<td>110 (86.6)</td>
<td>89 (95.7)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*Comparison of liver stiffness measurements between patients with and without NAFLD.
Continuous variables were expressed as median (IQR).
NAFLD, non-alcoholic fatty liver disease; LSM, liver stiffness measurement.
Key findings 1
Discussion

• Advanced fibrosis was prevalent in NAFLD patients with CAD (13.4%)
  – More prevalent compared with the general population (3.7% according to CUHK study)

• Two major mechanisms
  – Metabolic syndrome
  – Possible independent link btw liver fibrosis & CAD
    • To be discussed in the following sections
Key findings 1

Discussion

• Metabolic syndrome is much more common amongst CAD patients c/w general population
  – Only 20.3% of subjects in the general population study by Wong et al. had metabolic syndrome, compared to 72.9% in our study of CAD patients
  – Even if we compared only patients with NAFLD, there was a difference of 47.3% and 89.1% in the prevalence of metabolic syndrome between the two studies
Key findings 1

Discussion

• As metabolic syndrome is a strong independent predictor of the presence of NASH in patients with NAFLD, more NAFLD patients from our study were likely to have underlying NASH which had a higher chance of progression to advanced fibrosis or cirrhosis c/w patients with simple steatosis

Key findings 1
Discussion


**Table 4. Histopathologic Grading of Liver Biopsies in NAFLD Patients According to the Presence of the Metabolic Syndrome**

<table>
<thead>
<tr>
<th></th>
<th>With Metabolic Syndrome (n = 51)</th>
<th>Without Metabolic Syndrome (n = 112)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty infiltration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>23 (45%, 31-58)</td>
<td>65 (58%, 48-66)</td>
<td>.306</td>
</tr>
<tr>
<td>Moderate</td>
<td>20 (39%, 26-52)</td>
<td>33 (29%, 21-38)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>8 (16%, 7-27)</td>
<td>14 (12%, 7-19)</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>6 (12%, 5-22)</td>
<td>46 (41%, 32-50)</td>
<td>.0005</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perisinusoidal/pericellular</td>
<td>7 (14%, 6-25)</td>
<td>21 (19%, 12-26)</td>
<td></td>
</tr>
<tr>
<td>Periportal</td>
<td>21 (41%, 28-54)</td>
<td>28 (25%, 17-33)</td>
<td></td>
</tr>
<tr>
<td>Bridging</td>
<td>14 (27%, 16-40)</td>
<td>16 (14%, 9-21)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3 (6%, 1-15)</td>
<td>1 (1%, 0-4)</td>
<td></td>
</tr>
<tr>
<td>Necroinflammation</td>
<td>3 (6%, 2-15)</td>
<td>18 (16%, 10-23)</td>
<td>.031</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>17 (33%, 21-46)</td>
<td>45 (40%, 31-49)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>29 (57%, 42-69)</td>
<td>49 (44%, 34-53)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (4%, 1-12)</td>
<td>0 (0%, 0-2)</td>
<td></td>
</tr>
</tbody>
</table>
Key findings 1

Discussion

• Similar findings in the literature - Metabolic syndrome has been shown to be associated with a higher risk of advanced fibrosis in NAFLD patients.
Key findings 1

Discussion

• Chances of advanced disease (advanced fibrosis/cirrhosis) in NAFLD depends on the duration of ‘metabolic overload’

AASLD 2012 guideline on the diagnosis and management of NAFLD
**Key findings 1**

**Discussion**

![Graph showing the prevalence of NAFLD in patients with different number of components of metabolic syndrome.](image)

**Figure 4:** Prevalence of NAFLD in patients with different number of components of metabolic syndrome.
Figure 5: Prevalence of advanced fibrosis in NAFLD patients having valid LSM, with different number of components of metabolic syndrome.
Key findings 1

Discussion

• Implications: Consider screening for NAFLD and NAFLD with advanced fibrosis amongst CAD patients, especially those with multiple components of metabolic syndrome present
  – Good non-invasive tests like ultrasonography and transient elastography are readily available

• So is the relation between CAD and NAFLD simply because CAD patients have multiple metabolic risk factors?
### Key findings 2

**Table 6: Factors associated with significant coronary artery disease**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Significant CAD</th>
<th>Mild CAD</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>181</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>NAFLD, n (%)</td>
<td>117 (64.6)</td>
<td>20 (36.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>21 (15-29)</td>
<td>21 (14-26)</td>
<td>0.60</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (56-74)</td>
<td>63 (58-73)</td>
<td>0.54</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>141 (77.9)</td>
<td>31 (56.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.9 (23.3-28.2)</td>
<td>25.6 (23.1-28.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.0 (86.3-99.0)</td>
<td>91.0 (85.0-97.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>100 (55.2)</td>
<td>18 (32.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>129 (71.3)</td>
<td>43 (78.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 (116-145)</td>
<td>132 (115-145)</td>
<td>0.97</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68 (61-76)</td>
<td>68 (61-77)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
## Key findings 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Significant CAD</th>
<th>Mild CAD</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>81 (44.8)</td>
<td>15 (27.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.7 (5.0-6.9)</td>
<td>5.3 (4.9-6.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>Haemoglobin A1c (%)</td>
<td>6.2 (5.8-6.9)</td>
<td>6.1 (5.7-6.5)</td>
<td>0.089</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.0 (3.6-4.5)</td>
<td>4.3 (3.7-4.6)</td>
<td>0.058</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.2 (1.9-2.6)</td>
<td>2.3 (2.0-2.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.0 (0.9-1.2)</td>
<td>1.2 (1.1-1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.3 (1.0-1.8)</td>
<td>1.1 (0.9-1.5)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

**Independent factors associated with significant coronary artery disease in multivariate analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>2.24 (1.10-4.57)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

*Comparison of clinical characteristics between patients with significant CAD and mild CAD.

2 Defined according to the metabolic syndrome criteria by International Diabetes Federation in 2009.

3 Covariates included NAFLD, male gender, smoking history, diabetes mellitus, fasting glucose, haemoglobin A1c, total cholesterol, HDL-cholesterol and triglyceride (Hosmer and Lemeshow goodness-of-fit test; $\chi^2=9.471$, df=8, p=0.304).

Continuous variables were expressed as median (IQR).

CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
### Independent factors associated with significant multi-vessel coronary artery disease in multivariate analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>1.89 (1.01-3.54)</td>
<td>0.046</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.00-1.06)</td>
<td>0.038</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.26 (1.06-4.80)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*Comparison of clinical characteristics between patients with and without significant multi-vessel CAD.

1 Defined according to the metabolic syndrome criteria by International Diabetes Federation in 2009.

1 Covariates included NAFLD, age, male gender, diabetes mellitus, fasting glucose, haemoglobin A1c, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride ( Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 6.180$, df=8, p=0.627).

Continuous variables were expressed as median (IQR).

CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Key findings 2
Discussion

• NAFLD is an independent predictor of significant CAD and significant multi-vessel CAD (independent of other demographic and metabolic factors)
  – Our study provided additional local data and uses the definition of ≥70% stenosis to define significant CAD (c/w ≥50% used in CUHK study)

• This has been shown in a number of recent studies in the literature
Chronic inflammation
(e.g., increases in C-reactive protein, interleukin-6, tumor necrosis factor α, and other acute-phase proteins)

Hypercoagulation and hypofibrinolysis
(e.g., increases in fibrinogen, factor VII, plasminogen activator inhibitor 1, and other coagulation factors)

Atherogenic dyslipidemia
(e.g., increased triglycerides, decreased HDL cholesterol, increased small, dense LDL cholesterol, postprandial lipemia)

Dysglycemia and (hepatic) insulin resistance

Atherothrombosis
Independent factors associated with significant coronary artery disease amongst NAFLD patients with valid LSM, in multivariate analysis*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM (kPa)</td>
<td>1.37 (1.01-1.86)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

*Comparison of clinical characteristics between patients with significant CAD and mild CAD, amongst patients with NAFLD and valid LSM.

2 Defined according to the metabolic syndrome criteria by International Diabetes Federation in 2009.

3 Covariates included LSM, hypertension ², total cholesterol and HDL-cholesterol (Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 5.691$, df=8, p=0.682).

Continuous variables were expressed as median (IQR).

NAFLD, non-alcoholic fatty liver disease; LSM, liver stiffness measurement; CAD, coronary artery disease; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Key findings 3

Discussion

• Possible independent link exists between liver fibrosis & significant CAD

• As in a few small studies in literature
  – Multi-vessel CAD associated with LSM >7kPa..
    
  
  – Liver fibrosis score on histology in NAFLD is the only *independent* predictor of impaired coronary flow reserve..
    
    *Atherosclerosis* 2010;211:182-6.
Key findings 3

Discussion

• Potential mechanism: adipokines
  – Adipokines = hormones released from adipocytes
  – Adiponectin is anti-fibroegenic in liver and anti-atherogenic in the heart
  – The action of leptin is *vice versa*
  – Hypo-adiponectinaemia has been shown to be an *independent* predictor of advanced fibrosis in NAFLD, as well as an *independent* predictor of CAD
  – Association of high leptin with liver fibrosis & CAD have been consistently reported
Key findings 3

Discussion

Adiponectin

↓ glucose output
↓ fat accumulation
↓ inflammation

↑ glucose uptake
↑ fat accumulation
↑ energy expenditure

↓ inflammation
↓ endothelial adhesion
↓ foam cell formation

Protection from:
- Insulin-resistance
- Type 2 diabetes
- Coronary artery disease
Key findings 3
Discussion

- The adipokine profile of low adiponectin and high leptin has been shown to be independently associated with NAFLD in our local Chinese population.

Wong VW et al. Metabolic and adipokine profile of Chinese patients with NAFLD. *Clin Gastroenterol Hepatol* 2006;4:1154-61
Limitations of the study

- Single-centre, cross-sectional study
- Relatively small sample size
- NAFLD not biopsy proven
- Positive predictive value of transient elastography for advanced fibrosis in NAFLD, using the cutoff of 9.6 kPa, was only modest at 72.4%
- CAP/MR spectroscopy were not available
- XL probe was not available
Conclusion

• Advanced fibrosis by transient elastography is more prevalent in NAFLD patients with angiographically proven CAD compared with the general population, especially in those with multiple components of metabolic syndrome

• Targeted screening on this high risk group can be considered to avoid missing this important yet asymptomatic disease
Acknowledgement
Thank you for being here :)