Welcome to our December 2016 Newsletter!

The year of 2016 has proven to be another fruitful year for The Hong Kong Society of Gastroenterology in promoting the advancement of gastroenterology, with the organization of two successful Scientific Meetings in March and August. The Society also continued supporting the Medical Multispecialty Mega Conference and the IDD Forum. Moreover, two issues of the Society’s newsletter containing professional scientific updates, Society news and highlights of major events were published during the year.

On behalf of the Society, I wish to express my gratitude to Dr. Wai-Fun Luk for organizing the Annual General Meeting cum Scientific Meeting 2016, Dr. Jodis T.W. Lam for organizing the 18th Joint Annual Scientific Meeting, Professor Wai-Keung Leung for editing the two newsletters, Professor Ernst J. Kuiper, Professor Ping-Hong Zhou, Professor Siew C Ng, Dr. Wing-Yan Mak and Dr. Joulen Yue-Leung Lau for their scientific updates in this newsletter; all fellows and members for attending the scientific meetings, and friends from the pharmaceutical industry for their generous sponsorship and support.

Last but not least, may I remind you of the Asian Pacific Digestive Week Congress which will be held in Hong Kong on 23-26 September 2017. We look forward to seeing you all during the Congress for a valuable and enjoyable experience.

The next newsletter will be published in June 2017.

Best wishes for a merry Christmas and a happy new year.

Professor Justin C. Y. Wu
President, The Hong Kong Society of Gastroenterology

Risk for upper gastrointestinal cancer: Implications for intervention and surveillance

Nearly a quarter of all human cancers arise in the gastrointestinal (GI) tract. Despite a decrease in GI cancer-related deaths in the past two decades, cancers of the upper GI tract (including stomach cancer and esophagus cancer) are still associated with high mortality rates worldwide.¹

Neoplastic lesions and GI cancer
Prefector lesions such as atrophic gastritis, intestinal metaplasia and dysplasia precede most gastric cancer and can serve as targets for detection, intervention and surveillance. Patients with premalignant gastric lesions were shown to have an increased risk...
of gastric cancer, with the risk affected by the stage and distribution of the precursor lesions. Intervention and surveillance are therefore relevant management strategies for patients with advanced gastric and esophageal lesions.

**Intervention strategies**

Modification of risk factors associated with precursor lesions may have a positive impact on the incidence of gastric cancer. For example, tobacco control together with *Helicobacter pylori* reduction were shown to account for a significant proportion of the decline of intestinal-type noncardia gastric adenocarcinoma (NCGA) incidence in the USA. A meta-analysis of randomized controlled trials also showed that *H. pylori* eradication (especially in combination with antioxidants or vitamins) significantly reduced the incidence of gastric cancer compared with placebo or no treatment in infected Asian individuals who were otherwise healthy and asymptomatic. Interestingly, further analysis in the same study showed that there was no significant impact of *H. pylori* eradication on the progression rate of invasive gastric cancer in subjects who already have pre-neoplastic lesions.

For patients with Barrett’s esophagus (BE), intervention strategies include the use of proton pump inhibitors (PPI), nonsteroidal anti-inflammatory drugs (NSAIDs) and statins (all have been shown to reduce the risk of neoplastic progression and the incidence of esophageal adenocarcinoma [EAC]). Radiofrequency ablation, which was associated with a high rate of complete eradication of dysplasia and intestinal metaplasia and a reduced risk of disease progression.

**Surveillance & screening**

With the development and advancement of therapeutic endoscopy, surveillance and screening have become standard management of patients at risk for esophago-gastric cancer.

The Kyoto global consensus report on *H. pylori* gastritis stated that "*H. pylori* eradication may not completely eliminate the risk of gastric cancer. Patients that remain at risk, as defined by the extent and severity of atrophy, should be offered endoscopic and histological surveillance." Similarly, European guidelines on the management of patients with precancerous conditions and lesions in the stomach recommended that patients with extensive atrophy and/or intestinal metaplasia be offered surveillance at 3-year intervals.

A previous study on the effectiveness of endoscopic surveillance of premalignant gastric lesions showed that annual surveillance can detect the majority of new tumours at an early stage, resulting in significant improvement in the survival of patients with atrophic gastritis or intestinal metaplasia. Significant benefit in cancer stage at diagnosis was also observed in GI cancer patients who have received endoscopy screening compared to those who never received screening, with data suggesting that family members of gastric cancer patients may benefit from screening intervals of under 3 years.

A recent study showed that longer esophagogastroduodenoscopy time (>7 minutes) increased detection of neoplastic lesions by 3.4-fold during diagnostic upper GI endoscopy. Other recent evidence suggests that serum pepsinogen screening and endoscopy are potential cost-effective strategies in reducing NCGA mortality in high-risk smokers, and nanoarray analysis of exhaled breath may be an effective non-invasive screening tool for gastric cancer and surveillance of related precancerous lesions.

In addition to early detection of gastric lesions, endoscopic surveillance is also useful for early detection of EAC in patients with BE. However, BE patients are at a low risk of malignant progression and are predominantly associated with non-EAC related mortality (overall EAC incidence: 6.3/1000 person-years of follow-up), which undermines the cost-effectiveness of surveillance in these patients.

![Figure 1. *H. pylori* eradication and gastric cancer prevention](attachment:image-url)

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Risk ratio (95% CI)</th>
<th>Weight</th>
<th>Risk ratio (95% CI)</th>
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<td><em>H. pylori</em> eradication</td>
<td>Control</td>
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<td></td>
<td></td>
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<td>Correa 2000</td>
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<td>You 2004-Ma 2012</td>
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<td>Total</td>
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<td>76/3203</td>
<td>100.0</td>
<td>0.66 (0.46 to 0.95)</td>
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Test for heterogeneity: $\chi^2=0.60, \chi^2=3.62, df=5, p=0.60, I^2=0%$

Test for overall effect: $z=2.27, p=0.02$

With antioxidants or vitamins:

![Figure 2. Surveillance and early detection of EAC](attachment:image-url)

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Risk ratio (95% CI)</th>
<th>Weight</th>
<th>Risk ratio (95% CI)</th>
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<tr>
<td>Control</td>
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<td>Correa 2000</td>
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<td>Total</td>
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<td>100.0</td>
<td>0.52 (0.31 to 0.87)</td>
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</tbody>
</table>

Test for heterogeneity: $\chi^2=0.00, \chi^2=0.44, df=1, p=0.51, I^2=0%$

Test for overall effect: $z=2.49, p=0.01$

References

Cancer and infection in IBD: What should we tell our patients?

The incidence of inflammatory bowel disease (IBD) has increased by 30-fold in the last three decades according to data from the Hong Kong IBD Registry. The trend is predicted to continue to rise. Various IBD-related complications may lead to mortality, including infection/sepsis, cancer, thromboembolic events and post-operative complications. Minimizing the risk of infection and cancer in IBD patients has become an important treatment goal in IBD. Physicians need to counsel patients of such risks and weigh them against the potential benefits of IBD treatment.

“The concurrent use of steroids, thiopurine and infliximab is one of the major risk factors for opportunistic infections among IBD patients.”

Immunosuppression and infection risk
The increasing use of corticosteroids, immunosuppressants and biologics (such as anti-tumor necrosis factor [TNF] agents) in the treatment of IBD has led to an increased incidence of opportunistic infections and reactivation of latent tuberculosis infection (LTBI). It has been shown that the concurrent use of steroids, thiopurine and infliximab is one of the major risk factors for opportunistic infections among IBD patients, in addition to age (>50 years), malnutrition and comorbidities. However, it is interesting to note that anti-integrins (a new class of IBD medication) do not seem to be associated with an increased risk of infection in patients with ulcerative colitis.

“The concurrent use of steroids, thiopurine and infliximab is one of the major risk factors for opportunistic infections among IBD patients.”

Screening for LTBI before anti-TNF therapy is important as a high incidence of TB has been shown in patients receiving infliximab therapy. Screening for hepatitis B virus (HBV) and human papillomavirus (HPV) should also be considered as these are associated with increased infection rates in IBD patients who are on immunomodulators.

“Minimizing the risk of infection and cancer in IBD patients has become an important treatment goal in IBD.”

Risk of malignancy
IBD patients have a 5.7-fold higher risk of colorectal cancer, more aggressive lesions and earlier disease onset compared with the general population. IBD medications, such as immunomodulators and anti-TNFs, are mainly associated with two types of cancer – lymphoma and skin cancer. Studies have shown that the use of thiopurines is associated with a 4 to 5.2-fold increase in the risk of lymphoma in IBD patients compared with those not on immunomodulators. Similarly, thiopurines and biologics were associated with an increased risk of skin cancer in IBD patients.

Despite their association with immunomodulators and anti-TNFs, lymphoproliferative disorders are rare in IBD patients and the absolute incidences of lymphoma and skin cancer are relatively low. It is difficult to determine the long-term risk of cancer in IBD patients as it is related to both disease severity and the immunosuppressive therapy given, which vary among patients.

Conclusion
Physicians should be aware of the increased risk of infection in IBD patients with the concurrent use of two or more immunosuppressants, especially when steroids are involved. Screening for HBV, TB and CDI is mandatory in IBD patients before the commencement of biologics.

Ultimately, physicians need to balance the potential benefits provided by therapeutics and the associated risk involved in the management of IBD, and provide counseling to patients accordingly.

References
Endoscopic submucosal dissection and full-thickness resection of gastric tumours

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Endoscopic mucosal dissection (ESD) was developed for en bloc resection of large oesophageal, gastric or colonic lesions. However, small perforations often occur if ESD is performed for submucosal tumours arising from the muscularis propria (MP) layer and/or those that occur in close proximity to the serosa. A new endoscopic technique has been developed that enables complete full-thickness resection of such tumours. Like peroral endoscopic myotomy, it uses a submucosal tunnel as an operating space and it is known as submucosal tunnelling endoscopic resection (STER).1,2

The technique ensures the maintenance of gastrointestinal integrity while also enabling en bloc resection for histological analysis.3 It involves four key steps: locating the tumour site by submucosal injection of indigo carmine or methylene blue; creating a submucosal longitudinal tunnel between the submucosal and muscular layers using a hook or hybrid knife (ending 1–2 cm distal to the tumour to ensure a satisfactory endoscopic view of the tumour and enough working space for resection); completely resecting the tumour under direct endoscopic visualization using an insulated-tip knife, hook knife, or hybrid knife (sometimes a dual channel gastroscope with a grasping forceps is used to pull the tumour into the submucosal tunnel and prevent it falling into the peritoneal cavity – the tumour is then removed using a snare); closing the mucosal incision site, most commonly with haemostatic clips.2 (Figure)

Endoscopic full-thickness resection (EFTR) is another relatively new minimally invasive technique for resecting intraluminal submucosal tumours originating from the MP; it is performed without laparoscopic assistance.3 Key steps involved in the procedure are similar to those for STER and include: making a deep (ie, as deep as the MP) circumferential incision around the lesion using the standard ESD technique with a hook knife; completing a full-thickness incision with a hook knife or insulated-tip knife; removing the tumour (including its surrounding MP and serosa) with a snare; closing the defect in the gastric wall with metallic clips.2,3

Closure of the wall defect is the key stage of the EFTR procedure as it is important for preventing peritonitis and subsequent surgical intervention.4 Although the use of endoclips is widely accepted, the effectiveness is dependent on the skill of the surgeon.5 A new technique has been developed that uses endoloops as well as metallic clips for repairing gastric defects and it has been proven to be a relatively safe and easy method for closing gastric defects following EFTR.4 Another option is a novel endoscopic suturing device – Overstitch.5 The device is fitted to a double-channel endoscope and advanced to the oesophagus where it is then used to place polypropylene sutures and close the defect. A case report has described its successful application in a 66-year-old woman, in whom it was used to close a 10 mm-diameter fistula.5

Figure. Key steps involved in the submucosal tunnelling endoscopic resection (STER) technique

A. mucosal incision
B. submucosal tunnelling
C. tumour resection
D. finish resection and haemostasis
E. mucosal closure

A=A mucosal incision is made proximal to the tumour; B=A submucosal tunnel is created proximal and 1-2 cm distal to the tumour; C=The tumour is resected under direct endoscopic view; D=Resection is completed and haemostasis is performed; E=Mucosal closure is achieved with haemostatic clips.

Treatment of chronic hepatitis C: The Hong Kong experience

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Chronic hepatitis C (CHC) infection affects more than 170 million people worldwide, with 3–4 million new infections detected every year. It accounts for 27% of liver cirrhosis and 25% of hepatocellular carcinoma (HCC) globally, and the economic burden increases more than 3-fold in hepatitis C virus (HCV)-positive patients with complications compared with HCV carriers.1,2

Management of CHC
Prompt identification of patients with CHC and early intervention are important in the management of the disease. Treatments that can achieve sustained virological response (SVR) can prevent the development of liver cirrhosis and reduce the risk of HCC.

References
There has been significant advancement in HCV treatment over the past two decades, with the use of interferon-free combinations of direct acting antivirals (DAAs) leading to SVR rates of greater than 90%. However, the high cost associated with DAAs, along with other barriers to treatment, remain a challenge in the management of CHC.

HCV infection in Hong Kong

The prevalence of HCV infection in Hong Kong is around 0.5% in the general population with the most common genotypes being G1b (64%) and G6 (24%). Blood transfusion is the major risk factor for HCV infection, accounting for 38% of the cases, followed by intravenous (IV) drug use (30%) and tattooing (25%).

Pegylated interferon-α (Peg-IFN-α) and ribavirin (RBV) combination therapy remains the standard treatment of CHC in Hong Kong, with an overall SVR rate of 54–63%, despite being associated with numerous side effects. Of note, the treatment uptake rate is relatively low in Hong Kong (eg, only 20% of IV drug users with CHC received treatment between 2009 and 2012).

Local data on CHC

Queen Elizabeth Hospital (QEH) carried out a retrospective review of all CHC cases referred from January 2002 to March 2014 to obtain the most updated local data on CHC. Among the 723 HCV-positive patients referred, 143 (19.8%) received combination therapy with Peg-IFN-α and RBV. Causes of low treatment uptake rate included patients’ concern about side effects, default on follow-up treatment, and presence of contraindications. The majority of treated patients acquired infection through blood transfusion (31%) and IV drug use (29%). The most common genotypes were G1, G1b and G6. The overall SVR rate was 72.7%, and patients with the G6 genotype achieved the best response towards combination therapy (SVR rate of 89.3% vs 62.5% in patients with the G1 genotype; p=0.008). Predictors of good treatment response included non-genotype 1 HCV infection, low baseline HCV RNA level, absence of Peg-IFN therapy history, and at least 80% completion rate of the recommended course of treatment.

Treatment side effects were documented in 126/143 patients (88.1%), the most common being anaemia, neutropenia, flu-like symptoms and rash. Presence of side effects was the main reason for premature discontinuation of treatment (44/143 patients, 30.8%) while dose reduction was required in 71/143 patients (49.7%). Three patients expired during the review period (one due to pneumonia, two due to HCC) and 10 patients developed HCC despite completion of combination therapy (seven patients had advanced fibrosis before treatment and six patients did not achieve SVR).

Future of CHC treatment

An ideal CHC treatment should achieve a high SVR rate (>95%) as SVR is associated with reduced liver-related complications, liver-related mortality, and all-cause mortality in HCV patients. An optimal treatment should also have pan-genotypic activity; involve a short treatment duration and a low pill burden; cause minimal or no side effects and drug-drug interactions; and be easily accessible to patients.

The advent of DAAs improved the efficacy (SVR rate >90%) and safety of CHC treatment, but these medications are costly. The Hospital Authority Formulary in Hong Kong has authorized the use of the DAA boceprevir since 2013 for patients with HCV infection (G1 genotype) who have failed previous combination therapy. Despite the approval and rapid development of DAAs, combination therapy with Peg-IFN-α and RBV remains the standard first-line treatment of CHC in Hong Kong due to its lower cost. Newer-generation DAAs that are more cost-effective have the potential to become the standard of care for CHC patients in the future.

References


Figure. SVR reduced mortality in HCV patients
Gastroparesis

Gastric emptying is a result of a highly coordinated series of motor activities, including movement of the antrum, pyloric relaxation, antroduodenal coordination, and relaxation of the duodenum. A deficiency in any one of these processes will lead to a delay in gastric emptying and the associated clinical syndrome called gastroparesis.

The majority of patients have idiopathic gastroparesis (gastroparesis without an identifiable cause). Some of the causes of gastroparesis are reversible (e.g., acute onset of disease after viral infection, poor glycemic control, medications) and should be considered before opting for invasive treatments.

Diagnosis

Gastroparesis is often misdiagnosed due to overlapping symptoms and clinical features with functional dyspepsia and other gastrointestinal (GI) disorders, such as rumination syndrome, anorexia nervosa and cyclic vomiting syndrome. At the Prince of Wales Hospital (PWH) in Hong Kong, high resolution impedance manometry is used to rule out rumination syndrome before invasive treatments are considered.

The following criteria are essential for accurate diagnosis of gastroparesis:
- Presence of symptoms
- Exclusion of gastric outlet obstruction
- Objective documentation of delayed gastric emptying

Scintigraphic solid gastric emptying is the standard method for diagnosis of gastroparesis. Gastric retention of solids at 4 hours after consumption is indicative of gastroparesis and topographic distribution of the isotope can help identify impaired component(s) of the gastric motor activity. Alternative tests include the 13C-octanoate breath test and a GI monitoring system involving a smart wireless motility capsule that can measure the pH, pressure and temperature in different parts of the digestive tract, enabling estimation of retention time of the capsule in the stomach.

Management

Many mechanisms are involved in the etiology of gastroparesis, rendering it difficult to identify treatment targets. Management options include:
- Replenishment of nutrition, fluids and electrolytes
- Optimization of glycemic control (for patients with concomitant diabetes)
- Dietary modification (to lessen burden on gastric digestion)
- Post-pyloric enteral alimentation
- Medications, including gastrokinetic and antiemetic agents

There are a number of gastrokinetic agents targeting different receptors in the stomach (e.g., dopamine D2 antagonist, cholinergic M1 agonist, 5HT4 agonist, motilin agonist and ghrelin agonist).1 Ghrelin agonist is a potent stimulant of appetite and gastric motility and was found to substantially reduce the frequency and severity of nausea and vomiting as well as overall gastroparesis symptoms.2 Most of the gastrokinetic agents are non-selective and can cross the blood-brain barrier leading to side effects. High-dose, long-term treatment with these agents may also lead to prolonged QT interval, necessitating electrocardiogram monitoring.

Gastric electrical stimulation (GES) may be considered for patients with symptoms refractory to medications, provided that the patient can afford the procedure and expertise is available. GES is an environmentally friendly procedure involving high-frequency, low-energy electrical stimulation. It may induce a direct antiemetic effect, increase antral contraction and gastric accommodation, and decrease pyloric tone and gastric hypersensitivity. A meta-analysis of clinical studies showed substantial benefits of high-frequency GES in the treatment of gastroparesis, although many of the involved studies lacked controls.3 At present, GES is approved by the US Food and Drug Administration only as a Humanitarian Use Device for patients with refractory symptoms.

There is currently a lack of evidence supporting the efficacy of endoscopic and surgical methods, and of acupuncture, in the treatment of refractory gastroparesis.

Treatment strategy at PWH

The management of gastroparesis at PWH (Figure) comprises symptom identification, exclusion of mechanical gastric outlet obstruction, diagnostic testing, dietetic and medical intervention, and screening for and treatment of psychiatric comorbidity. The latter is important as some of the nausea, vomiting and pain experienced by patients may be attributed to the supratentorial region of the brain rather than to the GI tract. If the disease persists, GES and other treatments, such as surgery and acupuncture, may be considered upon discussion with the patient.

References

Non-alcoholic fatty liver disease and advanced fibrosis by transient elastography in Hong Kong Chinese patients with angiographically proven coronary artery disease (Summary of Thesis 2015)

Background
Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease, both worldwide and in Hong Kong. About 10-33% of the population worldwide is affected, and in Hong Kong the population prevalence of NAFLD is 27.3%.1-2 It is even more common amongst patients with coronary artery disease (CAD).1 According to local studies of our general population, few NAFLD patients have advanced fibrosis.3,4 However, local data on the prevalence of advanced fibrosis in NAFLD patients with CAD is lacking. As patients with CAD often have multiple metabolic risk factors, they may have a higher chance of progression from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and advanced fibrosis.

There is an increasing awareness of NAFLD as an independent risk factor of CAD. A large population-based study in Korea involving 4023 subjects found that NAFLD was significantly associated with increased coronary artery calcification scores, independent of classical coronary risk factors and computed tomography-measured visceral adiposity.4 The 10-year risk of developing CAD, as estimated by the Framingham risk score, was also found to be higher amongst NAFLD subjects compared to their non-NAFLD counterparts, independent of classical risk factors in another Korean study.4 A local study found that NAFLD was associated with significant CAD, using 50% stenosis of any one of the major coronary vessels as the cut-off, independent of other metabolic risk factors.3

The primary objective of this study was to determine the prevalence of advanced fibrosis by transient elastography in NAFLD patients with angiographically proven CAD. This study also investigated the role of NAFLD as a predictive factor of significant and more complex CAD in Hong Kong Chinese population.

Methods
Subjects and study design
This cross-sectional study recruited all adult Chinese patients (age ≥18 years) who underwent elective or emergency coronary angiogram for evaluation of suspected CAD at Pamela Youde Nethersole Eastern Hospital (PYNEH). The study was conducted over a 9-month period from 10 February 2014 to 10 November 2014. Patients with normal coronary arteries on coronary angiogram were excluded.

Patients with excessive alcohol consumption (≥140 grams/week in men and ≥70 grams/week in women) over the one-year period prior to the study, and patients on medications which could cause secondary hepatic steatosis were excluded. Patients with positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), anti-mitochondrial antibody, an anti-nuclear antibody (ANA) titer of >1:160, or serum ceruloplasmin concentration of <0.14g/L were also excluded.

In addition, patients with contraindications to transient elastography such as pacemaker or implantable cardioverter defibrillator in-situ, patients with ascites or on continuous ambulatory peritoneal dialysis, as well as those with known conditions which could cause falsely elevated liver stiffness measurement (LSM) (i.e. raised alanine aminotransferase to more than 5 times the upper limit of normal, biliary obstruction, hepatocellular carcinoma, moderate to severe tricuspid regurgitation, hepatic congestion on ultrasonography) were excluded. Patients who refused or were unable to consent for our study were also excluded. The study protocol was approved by the Hong Kong East Cluster Ethics Committee. Written informed consent was obtained from all recruited patients prior to their discharge after coronary angiogram.

Workup
Patients were admitted to the medical day ward for workup within 2 weeks from the date of coronary angiogram. Anthropometric parameters and blood pressure (BP) were measured.

Ultrasonography is an accurate test for the diagnosis of fatty liver, with sensitivity of 84.8% and specificity of 93.6% for detection of ≥20-30% hepatic steatosis compared to histology.6 Ultrasonography of abdomen was performed by the principal investigator who had performed over 100 abdominal ultrasonography examinations before this study. The ultrasonography findings were verified by a senior hepatologist. Ultrasonography images were captured and saved as hard copies for documentation. The diagnosis of fatty liver was based on at least two out of three ultrasonographic findings: (1) diffusely increased echogenicity of liver (greater than that of renal cortex or spleen); (2) hepatic vascular blurring; and (3) deep attenuation of ultrasound signal.7 Patients were also screened for any parenchymal liver diseases, cirrhotic changes, space-occupying lesions, biliary obstruction and hepatic congestion. Any splenomegaly, portal vein dilatation and abnormal flow direction of portal vein by Doppler ultrasonography were noted.

Transient elastography was then performed by an experienced gastrointestinal subspecialty nurse who was blinded to the clinical data. The standard M probe was used, as the XL probe was not available. The M probe had comparable diagnostic accuracy to XL probe in the majority of patients.8 The median value out of ten successful LSMs was taken as the liver stiffness. The result was considered valid if ten successful measurements were obtained, the ratio of interquartile range to the median value was less than 30% and at least two values were excluded. The median value of each patient was recorded.

The prevalence of NAFLD increased with the number of major coronary stents placed. The prevalence of NAFLD increased to 70% with ≥3 stents placed to the target coronary arteries.

Discussion
Patients with NAFLD had higher median LSM than their counterparts (92.7% vs. 93.9%, p=0.71). Patients with invalid or failed LSMs had higher median BMI (invalid/failed LSM median BMI 30.8 vs. 27.5, p=0.02). The prevalence of advanced fibrosis by transient elastography in NAFLD patients with CAD was 24.2%.

Patients with and without NAFLD (92.7% vs. 93.9%, p=0.71). There was no significant difference in the prevalence of advanced fibrosis by transient elastography in patients with and without diabetes mellitus (65.7% vs. 48.5%, p=0.008). The prevalence of NAFLD increased with the number of major coronary stents placed. Patients with additional components of metabolic syndrome present had significantly increased coronary artery calcification scores, independent of classical coronary risk factors and computed tomography-measured visceral adiposity.

Patients had elevated ALT level above the normal cutoff. The prevalence of NAFLD increased with the number of major coronary stents placed. The prevalence of NAFLD increased to 24.2% in those having all five components. Again, a significant association of NAFLD with significant CAD was found.

Patients were divided into two groups according to the presence of diabetes mellitus. The prevalence of advanced fibrosis by transient elastography in patients with diabetes mellitus was 23.4% compared to 18.4% in those without diabetes mellitus (p=0.04). The prevalence of NAFLD increased with the number of major coronary stents placed. The prevalence of NAFLD increased to 70% with ≥3 stents placed to the target coronary arteries.

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defined as ≥70% of stenosis in all three major coronary arteries. All patients without significant CAD were classified as mild CAD in our study.

All patients underwent venous blood taking on the next day following ultrasonography and transient elastography, after overnight fasting of 8 hours. The normal serum alanine aminotransferase (ALT) cutoff used was ≤30 IU/L in men and ≤19 IU/L in women. Patients with fatty liver detected on ultrasonography would receive additional tests including HBsAg, anti-HCV, ANA titer and serum ceruloplasmin level. For patients with advanced fibrosis on transient elastography, anti-mitochondrial antibody and iron profile were also checked.

The diagnosis of NAFLD with advanced fibrosis was based on (1) fatty liver on ultrasonography; (2) valid LSM ≥9.6 kPa by transient elastography; (3) no evidence of hepatic congestion on ultrasonography; and (4) exclusion of alcoholic, viral, autoimmune and metabolic causes of chronic liver diseases. The clinical diagnosis of metabolic syndrome was made according to the International Diabetes Federation criteria in 2009, with ethnicity-specific waist circumference threshold for abdominal obesity used for Asians.

Statistical analysis
Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 16.0 software. Categorical variables were expressed as frequency and percentage, and compared between groups by the χ² test or the Fisher’s exact test as appropriate. Continuous variables were expressed as median with interquartile range, and compared by the Mann-Whitney U test. Factors which approached significance (p<0.2) in univariate analysis were included in multivariate analysis. Binary logistic regression was done to identify independent factors associated with NAFLD, significant CAD and multi-vessel CAD. A two-sided p-value of less than 0.05 was regard as statistically significant.

Results
A total of 526 patients underwent coronary angiography over the period from 10 February 2014 to 10 November 2014 for suspected CAD. After exclusion of patients with excessive alcohol use, chronic viral hepatitis and other aforementioned conditions, 250 patients were recruited into the study. Another 14 patients were excluded after workup – they were either HBsAg positive, anti-HCV positive, ANA titer >1:160, or with features of hepatic congestion on ultrasonography. In the end, 236 patients were included in the final analysis (Figure 1).

The median age of the patients was 65 years (range, 36-85 years) and 172 (72.9%) patients were men (Table 1). The ethnicity of all patients was Chinese.

NAFLD
Out of a total of 236 patients, 137 (58.1%) had ultrasonography-diagnosed NAFLD. The prevalence of NAFLD amongst men and women were similar (58.1% vs. 57.8%, p=0.96). Patients in the NAFLD group were younger, with a lower median age (NAFLD vs. non-NAFLD = 63 years vs. 69 years, p<0.001). NAFLD patients had higher median BMI (26.3 kg/m² vs. 23.7 kg/m², p<0.001), larger median waist circumference (95.0 cm vs. 89.6 cm, p<0.001) and hip circumference (98.0 cm vs. 94.0 cm, p<0.001). In addition, they had higher median fasting plasma glucose (5.7 mmol/L vs. 5.2 mmol/L, p=0.034), and more commonly had impaired fasting glucose or diabetes mellitus (65.7% vs. 48.5%, p=0.008). Dyslipidaemia i.e. low plasma high-density lipoprotein cholesterol (77.4% vs. 40.4%, p<0.001) and hypertriglyceridaemia (67.9% vs. 36.4%, p<0.001) was more common among NAFLD patients. In addition, they had a higher median ALT level (24 IU/L vs. 18 IU/L, p<0.001), and more often had the level above normal cutoff (36.5% vs. 15.2%, p<0.001) (Table 1). HbA1c, systolic BP and diastolic BP were also associated with NAFLD in univariate analysis. With multivariate analysis, all the individual metabolic syndrome components independently predicted NAFLD, except hypertension (Table 2).

Table 2. Independent factors associated with NAFLD in multivariate analysis

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

Table 1. Study recruitment and participant flow.

<table>
<thead>
<tr>
<th>Exclusion</th>
<th>526 patients underwent coronary angiography for ACS/stable angina/CAD on non-invasive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 were of ethnicity other than Chinese</td>
<td>250 patients recruited into the study and received workup</td>
</tr>
<tr>
<td>37 had excessive alcohol consumption</td>
<td>236 patients included into the final analysis</td>
</tr>
<tr>
<td>2 had hepatitis C infection</td>
<td></td>
</tr>
<tr>
<td>7 were on methotrexate/tamoxifen</td>
<td></td>
</tr>
<tr>
<td>11 had pacemaker or ICD in-situ</td>
<td></td>
</tr>
<tr>
<td>18 had significant tricuspid regurgitation</td>
<td></td>
</tr>
<tr>
<td>Exclusion</td>
<td></td>
</tr>
<tr>
<td>60 found to have hepatitis B infection</td>
<td></td>
</tr>
<tr>
<td>5 found to have ANA&gt;1:160</td>
<td></td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CAD, coronary artery disease; ANA, anti-nuclear antibody; ICD, implantable cardioverter defibrillator; ALT, alanine aminotransferase; USG, ultrasonography; NAFLD, non-alcoholic fatty liver disease; LSM, liver stiffness measurement.
NAFLD with advanced fibrosis

220 (93.2%) out of 236 patients in the final analysis had a valid LSM by transient elastography. Eight (3.4%) patients had an invalid LSM and another 8 (3.4%) failed LSM acquisitions. Patients with invalid or failed LSMDs had higher median BMI (invalid/failed LSM vs. valid LSM = 28.3 kg/m² vs. 24.9 kg/m², p=0.008) and higher median waist circumference (invalid/failed LSM vs. valid LSM = 99.0cm vs. 91.5cm, p=0.044).

The proportion of patients with valid LSM was similar between patients with and without NAFLD (92.7% vs. 93.9%, p=0.71). Patients with NAFLD had higher median LSM than their non-NAFLD counterparts (6.1 kPa vs. 4.9 kPa, p<0.001). Of the 220 patients with valid LSM, 127 patients had NAFLD. Amongst the 127 NAFLD patients with valid LSM, the prevalence of advanced fibrosis by transient elastography was 13.4%, as defined by LSM ≥ 9.6 kPa (range, 10.0-25.7 kPa). Amongst the 93 non-NAFLD patients with valid LSM, the prevalence of advanced fibrosis was 4.3% only (p=0.035).

For the ultrasonographic findings of the 17 NAFLD patients with advanced fibrosis, cirrhotic changes were only present in one 78-year-old female patient, with corresponding LSM of 24.2 kPa. Splenomegaly was noted in the same patient. Altogether, three patients were found to have splenomegaly (range, 12.4-14.2cm), which was more common compared to those without advanced fibrosis (NAFLD with advanced fibrosis vs. NAFLD without advanced fibrosis = 17.6% vs. 0.9%, p=0.007). The portal vein diameter and flow direction by Doppler ultrasonography were all normal. All the 17 patients had preserved liver function, with normal total bilirubin (range, 9-23 µmol/L), prothrombin time (range, 9.4-11.5s), albumin (range, 40-47g/L) and albumin-to-globulin ratio (range, 1.2-1.8). Mild thrombocytopenia (138×10^9/L) was found in one patient with splenomegaly of 14.2cm. ALT level ranged from 14 to 41 IU/L, and 10 out of the 17 patients had elevated ALT level above the normal cutoff.

Ten NAFLD patients had an invalid LSM or failed LSM acquisitions. The prevalence of advanced fibrosis in these 10 patients, as estimated by the NAFLD fibrosis score, was 20%, using the higher cutoff value of 0.676.

Four patients had advanced fibrosis with LSM ≥9.6 kPa, but without evidence of NAFLD on ultrasonography. Parenchymal liver disease changes were present in all these patients, without cirrhotic changes or splenomegaly. Laboratory screening for other chronic liver diseases was unrevealing. These patients were classified as having cryptogenic advanced liver fibrosis.

### Table 1. Baseline clinical characteristics of 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>236</td>
<td>137</td>
<td>99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (56-74)</td>
<td>63 (55-70)</td>
<td>69 (61-75)</td>
<td></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>Current drinker, n (%)</td>
<td>35 (14.8)</td>
<td>21 (15.3)</td>
<td>14 (14.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypertension, n (%)</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, n (%)</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, n (%)</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>Triglycerides (mmol/L)</td>
<td>1.2 (0.9-1.8)</td>
<td>1.4 (1.0-1.9)</td>
<td>1.3 (0.8-1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</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 (9-16)</td>
<td>12 (9-16)</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>
<tr>
<td>Indication of angiogram, n (%)</td>
<td>102 (43.2)</td>
<td>59 (43.1)</td>
<td>43 (43.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>134 (56.8)</td>
<td>78 (56.9)</td>
<td>56 (56.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; CAD, coronary artery disease; IFG, impaired fasting glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease.

Defined according to the metabolic syndrome criteria by International Diabetes Federation in 2009, with ethnicity-specific criteria for abdominal obesity in Asians.

Current alcohol use of <140 grams/week in men and <70 grams/week in women.

Continuous variables were expressed as median (IQR).
NAFLD and CAD

The prevalence of NAFLD was much higher in patients with significant CAD, compared to those with mild CAD (64.6% vs. 36.4%, p<0.001). Patients with NAFLD more commonly had significant CAD (NAFLD vs. non-NAFLD = 85.4% vs. 64.6%, p<0.001) and multi-vessel CAD (52.6% vs. 34.3%, p=0.006) than those without NAFLD. The median degree of stenosis of each of the three major coronary arteries was significantly higher in patients with NAFLD. Significant stenosis of the left anterior descending artery (NAFLD vs. non-NAFLD, 67.2% vs. 44.4%, p<0.001) and left circumflex artery (47.4% vs. 32.3%, p=0.020) were also more common in patients with NAFLD. Not surprisingly, the need of placement of at least one or multiple (≥2) coronary stents was both higher in patients with NAFLD (Table 3).

The prevalence of NAFLD increased with the number of major coronary arteries with significant stenosis. NAFLD was found in 36.4% of patients with no significantly diseased vessel, while the prevalence increased to 69.2% amongst those with triple-vessel disease (Figure 2). The prevalence of NAFLD also showed an overall increasing trend with the number of coronary stents inserted (Figure 3).

By univariate analysis, a number of factors were associated with significant CAD, including NAFLD, male gender, smoking history, diabetes mellitus, fasting glucose, HbA1c, total cholesterol, high-density lipoprotein cholesterol and triglyceride. With multivariate analysis, only NAFLD (OR, 2.24; 95% CI, 1.10-4.57; p=0.027) predicted significant CAD independent of other demographic and metabolic risk factors (Table 4).

With regard to multi-vessel CAD, the following factors were associated with significant multi-vessel CAD in univariate analysis, including NAFLD, age, male gender, diabetes mellitus, fasting glucose, HbA1c, total cholesterol, triglyceride, low- and high-density lipoprotein cholesterol. With multivariate analysis, only NAFLD (OR, 1.89; 95% CI, 1.01-3.54; p=0.046), age (OR, 1.03; 95% CI, 1.00-1.06; p=0.038) and diabetes mellitus (OR, 2.26; 95% CI, 1.06-4.80; p=0.034) independently predicted multi-vessel CAD (Table 5).

Metabolic syndrome and NAFLD

Metabolic syndrome was significantly more common amongst patients with NAFLD than those without NAFLD (89.1% vs. 50.5%, p<0.001). All the individual components of metabolic syndrome, except hypertension, independently predicted NAFLD (Table 2).

In addition, the prevalence of NAFLD increased with the number of components of metabolic syndrome present. Only 14.3% of patients without any components of metabolic syndrome had NAFLD, but the prevalence increased progressively to 79.1% in those who had all five components. A sharp rise in prevalence of NAFLD was noted when the number of criteria defining metabolic syndrome was met, indicating a strong correlation of metabolic syndrome with NAFLD (Figure 4).

Table 3. Coronary angiogram findings in patients with and without NAFLD

<table>
<thead>
<tr>
<th>Coronary angiogram</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>LM stenosis degree (%)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.41</td>
</tr>
<tr>
<td>LM stenosis ≥50%, n (%)</td>
<td>18 (7.6)</td>
<td>10 (7.3)</td>
<td>8 (8.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>LAD stenosis degree (%)</td>
<td>70 (30-80)</td>
<td>70 (30-90)</td>
<td>50 (20-70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD stenosis ≥70%, n (%)</td>
<td>136 (57.6)</td>
<td>92 (67.2)</td>
<td>44 (44.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LCx stenosis degree (%)</td>
<td>35 (0-80)</td>
<td>40 (0-90)</td>
<td>30 (0-70)</td>
<td>0.042</td>
</tr>
<tr>
<td>LCx stenosis ≥70%, n (%)</td>
<td>97 (41.1)</td>
<td>65 (47.4)</td>
<td>32 (23.3)</td>
<td>0.020</td>
</tr>
<tr>
<td>RCA stenosis degree (%)</td>
<td>30 (0-70)</td>
<td>30 (0-80)</td>
<td>20 (0-70)</td>
<td>0.023</td>
</tr>
<tr>
<td>RCA stenosis ≥70%, n (%)</td>
<td>89 (37.7)</td>
<td>58 (42.3)</td>
<td>31 (31.3)</td>
<td>0.085</td>
</tr>
<tr>
<td>Significant CAD, n (%)</td>
<td>181 (76.7)</td>
<td>117 (85.4)</td>
<td>64 (64.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Significant multi-vessel CAD, n (%)</td>
<td>106 (44.9)</td>
<td>72 (52.6)</td>
<td>34 (34.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Stent insertion needed, n (%)</td>
<td>163 (69.1)</td>
<td>104 (75.9)</td>
<td>59 (59.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥2 coronary stents inserted, n (%)</td>
<td>94 (39.8)</td>
<td>62 (45.3)</td>
<td>32 (32.3)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Continuous variables were expressed as median (IQR).
NAFLD, non-alcoholic fatty liver disease; LM, left main stem coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery.

Figure 2. Prevalence of NAFLD in patients with significant stenosis (≥70%) of different number of major coronary arteries.

Figure 3. Prevalence of NAFLD in patients with different number of coronary stents inserted.
All the 17 NAFLD patients with advanced fibrosis had metabolic syndrome. 10.5% of NAFLD patients with three components of metabolic syndrome had advanced fibrosis, while the prevalence increased to 24.2% in those having all five components. Again, a sharp rise in prevalence of advanced fibrosis was noted when the number of criteria defining metabolic syndrome was met, suggesting a strong correlation of metabolic syndrome with advanced fibrosis in NAFLD (Figure 5).

Discussion

In this cross-sectional study involving 236 Hong Kong Chinese patients with CAD, 58.1% were found to have NAFLD by ultrasonography. The prevalence of advanced fibrosis by transient elastography was 13.4% amongst NAFLD patients with valid LSM, and even higher at 15.9% amongst NAFLD patients with significant CAD. NAFLD predicted significant CAD and multi-vessel CAD independent of other baseline demographic and metabolic risk factors. Finally, both the prevalence of NAFLD and advanced fibrosis in NAFLD increased with the number of underlying metabolic syndrome components.

To the best of our knowledge, this is the first study to date on the prevalence of advanced fibrosis by transient elastography in NAFLD patients specifically with angiographically proven CAD, using the well-validated LSM cutoff for local Chinese population. Furthermore, we adopted strict and consistent criteria in making the diagnosis of NAFLD to minimize the bias in case ascertainment.

Advanced fibrosis was prevalent in NAFLD patients with CAD

Few studies in the literature to date reported on the prevalence of advanced fibrosis by transient elastography in NAFLD patients with CAD. A study in Croatia found that 33.3% of NAFLD patients with CAD had LSM >7 kPa. However, the sample size was relatively small with only 45 NAFLD patients, and the LSM value of 7 kPa was not a locally validated cutoff value of advanced fibrosis. 9 Our study revealed that the prevalence of advanced fibrosis (defined by LSM ≥9.6 kPa) was 13.4% in NAFLD patients with CAD undergoing coronary angiography, and 15.9% in NAFLD patients with significant CAD, which were both much higher than 3.7% in NAFLD patients in the general Hong Kong Chinese population, as revealed in a local study. 2

Metabolic syndrome could account for the much higher prevalence of advanced fibrosis in NAFLD patients with CAD, compared with NAFLD patients in the general population. Only 20.3% of subjects in a local population study had metabolic syndrome, compared to 72.9% in our study which involved CAD patients. Even if we compared only patients with NAFLD in these two studies, there was a difference of 47.2% and 89.1% in the prevalence of metabolic syndrome. As the 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 compared to patients with simple steatosis. In fact, metabolic syndrome has been shown to be associated with a higher risk of advanced fibrosis in NAFLD patients in the literature. 12,13

### Table 4. 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>0.55</td>
</tr>
<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>CAD</td>
<td>2.24 (1.10-4.57)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

### Table 5. Factors associated with significant multi-vessel coronary artery disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Significant Multi-vessel CAD</th>
<th>No significant Multi-vessel CAD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>106</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>NAFLD, n (%)</td>
<td>72 (67.9)</td>
<td>65 (50.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>20 (14-29)</td>
<td>22 (15-28)</td>
<td>0.48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (57-75)</td>
<td>65 (56-72)</td>
<td>0.13</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>83 (78.3)</td>
<td>89 (68.5)</td>
<td>0.091</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8 (23.3-28.3)</td>
<td>25.2 (23-28.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91.8 (86.9-97.1)</td>
<td>91.5 (86.0-97.3)</td>
<td>0.62</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>57 (53.8)</td>
<td>61 (46.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>79 (74.5)</td>
<td>93 (71.5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132 (115-146)</td>
<td>130 (116-144)</td>
<td>0.83</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68 (61-75)</td>
<td>68 (62-77)</td>
<td>0.47</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>56 (52.8)</td>
<td>40 (30.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.9 (5.1-7.2)</td>
<td>5.3 (4.9-6.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Haemoglobin A1c (%)</td>
<td>6.3 (6.0-7.1)</td>
<td>6.1 (5.7-6.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.0 (3.6-4.4)</td>
<td>4.2 (3.7-4.6)</td>
<td>0.039</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>0.17</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.0 (0.8-1.2)</td>
<td>1.1 (0.9-1.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.3 (1.0-1.8)</td>
<td>1.2 (0.9-1.7)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**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>CAD</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>

Notes:
1. Defined according to the metabolic syndrome criteria by International Diabetes Federation in 2009.
2. 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: y² = 9.471, df = 8, p = 0.304).
3. 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: y² = 6.180, df = 8, p = 0.627).

Covariates included 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.
In our study, all the 17 NAFLD patients with advanced fibrosis had metabolic syndrome. The prevalence of advanced fibrosis by transient elastography in NAFLD patients increased with the number of metabolic syndrome components, when the number of criteria defining metabolic syndrome was met. A similar trend was found in a study from Australia,\textsuperscript{14} where the percentage of hepatic fibrosis on liver biopsy in NAFLD patients correlated significantly with increasing number of metabolic syndrome components as defined by the Adult Treatment Panel (ATP) III criteria, suggesting the correlation between liver fibrosis and metabolic syndrome. Although cirrhotic changes were only present on ultrasonography in one of the 17 patients with NAFLD and LSM ≥9.6 kPa, the actual number of patients with NAFLD and cirrhosis might be higher. Firstly, the best locally validated LSM cutoff value for NAFLD with F4 disease (i.e. cirrhosis) was 10.3 kPa.\textsuperscript{8} Amongst the 17 patients, 15 of them had F4 disease by this cutoff value, although the positive predictive value was 46% only.\textsuperscript{9} Therefore, up to seven of them may have the diagnosis of cirrhosis made if this cutoff value was taken. Secondly, apart from the one with cirrhotic changes on ultrasonography, two other patients had splenomegaly (12.5cm and 14.2cm respectively), and one of them had thrombocytopenia, indicating possible underlying portal hypertension and hypersplenism. Advanced fibrosis per se (without cirrhosis and portal hypertension) was unlikely to account for splenomegaly and thrombocytopenia in these patients. In fact, early cirrhotic changes on ultrasonography may be masked by the increased echogenicity of liver and hepatomegaly with fatty infiltration in NAFLD patients.

The actual prevalence of advanced fibrosis in NAFLD patients with CAD could be underestimated in our study. There were four patients with ‘cryptogenic advanced liver fibrosis’ in our study, with ultrasonography showing parenchymal liver disease changes only. Three of them were obese and one was overweight, and all of them had abdominal obesity. In addition, all of them had diabetes mellitus as well as metabolic syndrome, with 4.25 components of the syndrome on average. So all these four patients had multiple risk factors of NAFL and NASH with fibrosis progression, and it is possible that these patients had burnt-out NASH with residual advanced fibrosis. Furthermore, steatosis may be undetectable by ultrasonography because of severe fibrosis.\textsuperscript{11} In fact, NASH is believed to play a significant role in many patients with cryptogenic cirrhosis, especially those with underlying metabolic risk factors.\textsuperscript{16} Thus the actual prevalence of advanced fibrosis in NAFLD patients with CAD could be up to 16.0% in our study, if these patients indeed had burnt-out NASH with residual advanced fibrosis.

NAFLD and CAD

The overall prevalence of NAFLD in patients with CAD undergoing coronary angiogram in our study was 58.1%, comparable to a local study and two other Asian studies.\textsuperscript{17,18} In the past, NAFLD was regarded as a disease of the West. However, the prevalence was found to be similar at 60.6% in a Turkish study of comparable sample size and inclusion criteria to our study,\textsuperscript{19} showing that NAFLD is as important amongst CAD patients in the East. As from our study, the prevalence of NAFLD in CAD patients was almost twice of that found in the general population, which was quoted at 27.3% according to a local study.\textsuperscript{2}

The prevalence of NAFLD amongst patients with significant CAD and mild CAD was also very similar to the aforementioned local study;\textsuperscript{2} with the former group having a much higher prevalence of NAFLD. There were two reasons which could explain this phenomenon. Firstly, patients with significant CAD had multiple vascular risk factors and more often suffered from concomitant metabolic syndrome than patients with mild CAD in our study (77.9% vs. 56.4%, p = 0.002). Individual components of metabolic syndrome have been shown to be associated with NAFLD in our study and in previous studies.\textsuperscript{1,12} Secondly, NAFLD per se was an independent risk factor of significant CAD, as shown in our study and in several previous studies.\textsuperscript{1,7,18} Our study used ≥70% stenosis of any major coronary artery as the cutoff value of significant CAD, which was in accordance with the latest recommendations by the American College of Cardiology Foundation.\textsuperscript{20} On the contrary, the cutoff value of ≥50% stenosis has been used in many studies of similar design in the literature. The definition used in our study may be more practical, as it formed the basis for cardiologists to decide on the need of coronary stent insertion. As such, we proved that NAFLD remained to be an independent predictor of significant CAD, defined as ≥70% stenosis of any major coronary artery.

The independent association of NAFLD with markers of subclinical atherosclerosis was confirmed in a recent systematic review of 27 studies.\textsuperscript{21} NAFLD was independently associated with coronary artery calcification, a surrogate marker of coronary atherosclerosis.\textsuperscript{4} These support the theory that NAFLD is implicated in the pathogenesis of CAD. A number of potential mechanisms have been postulated, including theories involving inflammatory cytokines, very-low-density-lipoprotein, oxidative stress and coagulation imbalance.
Limitations
Our study has a few limitations. Firstly, it was a single-centre cross-sectional study at a local regional hospital, and the sample size was relatively small. Secondly, except for transient elastography, our study was conducted by a single investigator, thus blinding of clinical and laboratory data of the patients was imperfect. Thirdly, ultrasonography is less sensitive to detect mild hepatic steatosis of <20-30%, thus our results were likely to be conservative estimates of the actual prevalence of NAFLD amongst CAD patients. Finally, the positive predictive value of transient elastography for advanced fibrosis in NAFLD using the cutoff of 9.6 kPa was only modest at 72.4%. However, the same cutoff value has been used in a local study to determine the prevalence of advanced fibrosis in NAFLD patients in the general population.2

Future large-scale studies are needed to shed more light on the subject of NAFLD and advanced fibrosis in CAD patients. The use of transient elastography with XL probe and controlled attenuation parameter (CAP) may increase the proportion of patients with valid LSM and give a more objective measure of the degree of hepatic steatosis, respectively. With CAP, the correlation between the degree of hepatic steatosis and CAD can be studied. Histological correlation on patients with significant CAD after completion of dual anti-platelet therapy is also desirable in view of the modest positive predictive value of transient elastography.

Conclusion and implications
In conclusion, advanced fibrosis by transient elastography is prevalent in non-alcoholic fatty liver disease patients with angiographically proven coronary artery disease, especially in those with multiple components of metabolic syndrome. Targeted screening on this high risk group should be considered to avoid missing this important yet asymptomatic disease. With the high prevalence of NAFLD in patients with CAD, bedside ultrasonography screening for fatty liver is warranted. Transient elastography should be considered especially in those with metabolic syndrome. Timely diagnosis of NAFLD with advanced fibrosis allows intensive lifestyle modifications, close monitoring and screening for hepatocellular carcinoma to be implemented. Effective anti-fibrotic therapies are in development and may offer therapeutic options to those with advanced fibrosis in the future.

Acknowledgement
I would like to thank the Gastroenterology and Hepatology team, Department of Medicine, PYNEH, for their support and guidance on this study.

References
fibrosis on liver biopsy in NAFLD patients correlated significantly. Of them had F4 disease by this cutoff value, although the positive correlation of diabetes mellitus as well as metabolic syndrome, with 4.25 components of classical coronary risk factors and computed tomography (without cirrhosis and portal hypertension) was unlikely to cryptogenic cirrhosis, especially those with underlying metabolic syndrome.

A study from Australia, where the percentage of hepatic steatosis was higher amongst NAFLD subjects compared to the general population, found that the prevalence of diabetes mellitus was much higher in patients with coronary artery disease (CAD). According to local studies of our general population, few NAFLD patients had diabetes mellitus, compared with NAFLD patients in the general population. Only about 10-33% of patients had a validated LSM, with sensitivity of 84.8% and specificity of 93.6% for hepatocellular carcinoma, moderate to severe tricuspid regurgitation, and advanced fibrosis on transient elastography. There is an increasing awareness of NAFLD as an independent risk factor for coronary artery disease (CAD), defined as 70% stenosis of any major coronary artery.

The prevalence of NAFLD increased with the number of major criteria defining metabolic syndrome, compared to 72.9% in our study which involved CAD patients. Even if we compared only patients with NAFLD in these studies, a sharp rise in prevalence of advanced fibrosis was noted when the number of criteria defining metabolic syndrome was met. The prevalence of NAFLD was much higher in patients with CAD, compared with NAFLD patients in the general population. Only 36% of NAFLD patients had diabetes mellitus, compared with 72.9% in our study which involved CAD patients. Only about 10-33% of patients had a validated LSM, with sensitivity of 84.8% and specificity of 93.6% for hepatocellular carcinoma, moderate to severe tricuspid regurgitation, and advanced fibrosis on transient elastography.

The prevalence of NAFLD increased with the number of major criteria defining metabolic syndrome, compared to 72.9% in our study which involved CAD patients. Even if we compared only patients with NAFLD in these studies, a sharp rise in prevalence of advanced fibrosis was noted when the number of criteria defining metabolic syndrome was met. The prevalence of NAFLD was much higher in patients with CAD, compared with NAFLD patients in the general population. Only 36% of NAFLD patients had diabetes mellitus, compared with 72.9% in our study which involved CAD patients. Only about 10-33% of patients had a validated LSM, with sensitivity of 84.8% and specificity of 93.6% for hepatocellular carcinoma, moderate to severe tricuspid regurgitation, and advanced fibrosis on transient elastography.

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Organizer: Asian Pacific Association of Gastroenterology (APAGE), Asia Pacific Association for the Study of the Liver (APASL), Asian Pacific Society for Digestive Endoscopy (AP-SIDE) and ISDS Asian Pacific

Location: Hong Kong
Website: www.apdw2017.org

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Asian Pacific Digestive We...
Welcome! New Fellows and Members

**Fellow**

Dr. Kelvin Kwok Chai NG  
Clinical Associate Professor  
Department of Surgery  
The University of Hong Kong

Dr. Wai-Lun TAO  
Department of Medicine  
Yan Chai Hospital  
N.T., Hong Kong

**Member**

Dr. Wing-Yee CHENG  
Department of Medicine & Geriatrics  
Princess Margaret Hospital  
Kowloon, Hong Kong

Dr. Lung-Yi MAK  
Department of Medicine  
Queen Mary Hospital  
Hong Kong

Dr. Ronald Kin-Nam TONG  
Department of Medicine and Geriatrics  
Caritas Medical Center  
Kowloon, Hong Kong

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Coming Soon

The Hong Kong Society of Gastroenterology  
36th Annual General Meeting cum Scientific Meeting  
Thursday, 2 March 2017  
6:00 pm

Venue: Level 7, Cordis Hong Kong at Langham Place  
555 Shanghai Street, Mongkok, Kowloon  
Organizing Chairperson: Dr. Wai-Fan Luk

**Presentation of Honorary Fellowship by President, Professor Justin C.Y. Wu**

“From H.pylori to Colorectal Disorders: a Personal Perspective”  
Professor Kwong-Ming Fock  
Senior Consultant, Gastroenterology and Hepatology  
Division of Gastroenterology  
Department of Medicine  
Changi General Hospital  
Singapore

Case Discussion on Endoscopy in IBD  
Dr. Moe Kyaw  
Department of Medicine & Therapeutics  
The Chinese University of Hong Kong  
Prince of Wales Hospital  
Shatin  
Hong Kong

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Annual General Meeting

(More information will be available soon from www.hksge.org)
18th Joint Annual Scientific Meeting

Date: 28 August 2016

Venue: Cordis, Hong Kong at Langham Place, Kowloon

Organizing Chairperson: Dr. Jodis Ting-Wa Lam

Sponsored by: AbbVie, AstraZeneca, Ferring, Fujifilm, Gilead, Janssen, A.Menarini, MSD, Novartis, Otsuka, Sandoz of Novartis & Takeda

The 18th Joint Annual Scientific Meeting was successfully held on 28 August 2016 and attended by 267 healthcare professionals. The conference is an annual landmark scientific event jointly organized by six societies for gastrointestinal and hepatobiliary diseases in Hong Kong, namely The Hong Kong Society of Gastroenterology, Hong Kong Society of Digestive Endoscopy, Hong Kong Society for Coloproctology, The Hong Kong Association for the Study of Liver Diseases, The Hong Kong Society of Gastrointestinal Motility and the Hong Kong IBD Society.

There were 8 lectures covering hot topics in gastroenterology, hepatology, endoscopy and surgery delivered by renowned speakers. Guest speakers from overseas included Dr. George Webster from the U.K. and Dr. Marta Jimenez-Toscano from Spain. Other honorable local speakers included Dr. Kelvin Lam, Professor Wai-Keung Leung, Dr. Raymond Tang and Dr. Heyson Chan.

The program was stimulating. Some of the exciting topics included treatment of autoimmune liver diseases and management of primary sclerosing cholangitis; update of faecal microbiota transplantation; innovative surgical treatment of rectal cancer; management of serrated adenoma/polyp and recent advances in endoscopic biliary intervention and biologic therapy in IBD.

Interactive panel discussions were held at the end of each of the three symposia. Delegates participated actively throughout the discussions. This year’s meeting continued to provide a valuable platform for local and overseas gastrointestinal professionals and experts to exchange knowledge and share experience in different perspectives of GI diseases. It was proven to be an enjoyable and rewarding event.