Putting MAFLD into perspective
non-invasive evaluation and treatment

Jian-Gao Fan MD, PhD.
Department of Gastroenterology
Xinhua Hospital
Shanghai JiaoTong University School of Medicine
Shanghai 200092, China

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Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome

NAFLD & MetS

NAFLD is closely associated with features of MetS such as insulin resistance, hyperglycemia, obesity and dyslipidemia[1,2]

Patients with obesity, raised fasting glucose levels, T2D or other metabolic abnormalities have an increased risk of advanced fibrosis compared with those without metabolic abnormalities[1]

As advanced fibrosis is directly associated with liver-related events, metabolic abnormalities could predict a poorer long-term prognosis in patients with NAFLD[3]

Therefore, metabolic disorders should be considered when screening for liver fibrosis. However, the diagnostic performance, accessibility and cost-effectiveness of current non-invasive diagnostic measurements need to be improved

MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes.

1. Jinjuvadia R, et al. J Clin Gastroenterol 2018;51(2):160–166; 2. Vernon G, et al. Aliment Pharmacol Ther 2011;34(3):274–285; 3. Dulai PS, et al. Hepatol 2017;65(5):1557–1565.

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TOWARDS1 - study design and aims[1,2]

Observational, cross-sectional registry study conducted in 14 sites across mainland China

Patients aged 18–65 years with liver biopsy-proven NAFLD were enrolled

Demographic and anthropometric characteristics, medical history and metabolic disorders were collected at enrollment

Liver biopsy samples were collected for histopathological re-reading

Metabolic Disorders Combined with Non-invasive Tests to Screen Advanced Fibrosis in NAFLD[1]

Aim: Explore the role of metabolic disorders in screening for liver fibrosis

The pathologic relevance of metabolic criteria in patients with biopsy-proven NAFLD and metabolic dysfunction associated fatty liver disease: A multicenter cross-sectional study in China[2]

Aim: Evaluate the association between metabolic components and the pathological severity of NAFLD using biopsy samples and discuss the pathological relevance of the MAFLD diagnostic criteria

NAFLD, non-alcoholic fatty liver disease

1. Shi YW, et al. J Clin Transl Hepatol 2021; doi:10.14218/JCTH.2021.00058; 2. Yang RX, et al. Hepatobiliary Pancreat Dis Int 2021; doi:10.1016/j.hbpd.2021.06.002.

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Baseline demographics of enrolled patients

246 patients with biopsy-proven NAFLD were enrolled in the TOWARDS1 study

Baseline demographics of patients with and without MetS and of the total patient population

Variable	Patients with MetS* (n=133)	Patients without MetS* (n=113)	Total patient population (N=246)
Age in years (mean)	42	38	39
Male (n, %)	89 (67)	88 (78)	177 (72)
Hypertension (n, %)	42 (32)	14 (12)	56 (22.8)
Dyslipidemia (n, %)	35 (26)	22 (19)	57 (23.2)

*MetS consisted of central obesity plus any two of the following metabolic disorders: elevated triglyceride, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure and raised fasting glucose, according to the guideline from the International Diabetes Foundation (2005).
Shi YW, et al. J Clin Transl Hepatol 2021; doi:10.14218/JCTH.2021.00058.

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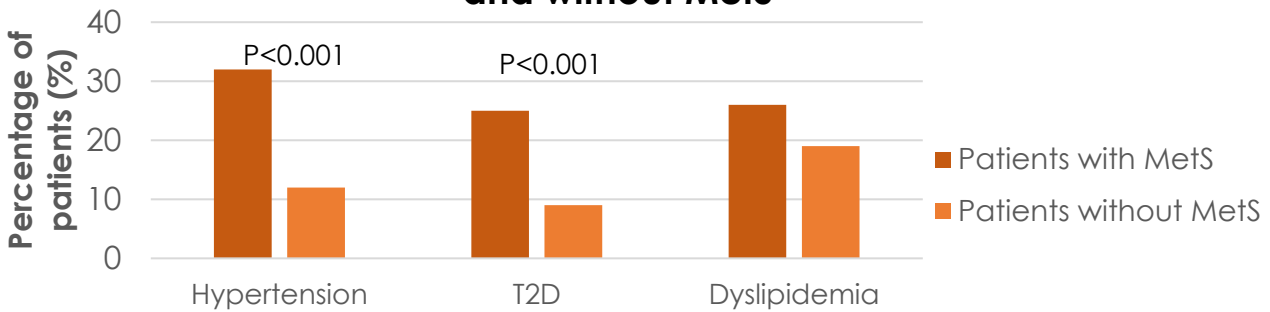
Clinical characteristics of enrolled patients

61% (n=151) of patients had moderate or severe steatosis, and **84%** (n=207) had NASH

- **31%** (n=76) of patients had significant fibrosis (≥F2) and **15%** (n=38) had advanced fibrosis (F3&F4)

- Approximately **76%** (n=178) of patients had central obesity, and **54%** (n=133) met the criteria for MetS*

Differences in clinical characteristics between patients with and without MetS



Clinical Characteristic	Patients with MetS	Patients without MetS	P-value
Fasting plasma glucose (mmol/L) (mean, ± SD)	5.9 ±1.8	5.1 ±0.9	<0.001
HbA1c (%) (mean, ± SD)	6.37 ±1.69	5.64 ±0.7	<0.001
HOMA-IR (mean, range)	3.8 (2.6, 5.6)	2.4 (1.7, 3.5)	<0.001
TG (mmol/L) (mean, range)	1.90 (1.44, 2.62)	1.42 (1.06, 2.05)	<0.001
HDL-C (mmol/L) (mean, ± SD)	1.01 ± 0.22	1.13 ± 0.24	<0.001

*MetS consisted of central obesity plus any two of the following metabolic disorders: elevated triglyceride, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure and raised fasting glucose, according to the guideline from the International Diabetes Foundation (2005). HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TG, triglycerides; T2D, type 2 diabetes.

Shi YW, et al. J Clin Transl Hepatol 2021; doi:10.14218/JCTH.2021.00058.

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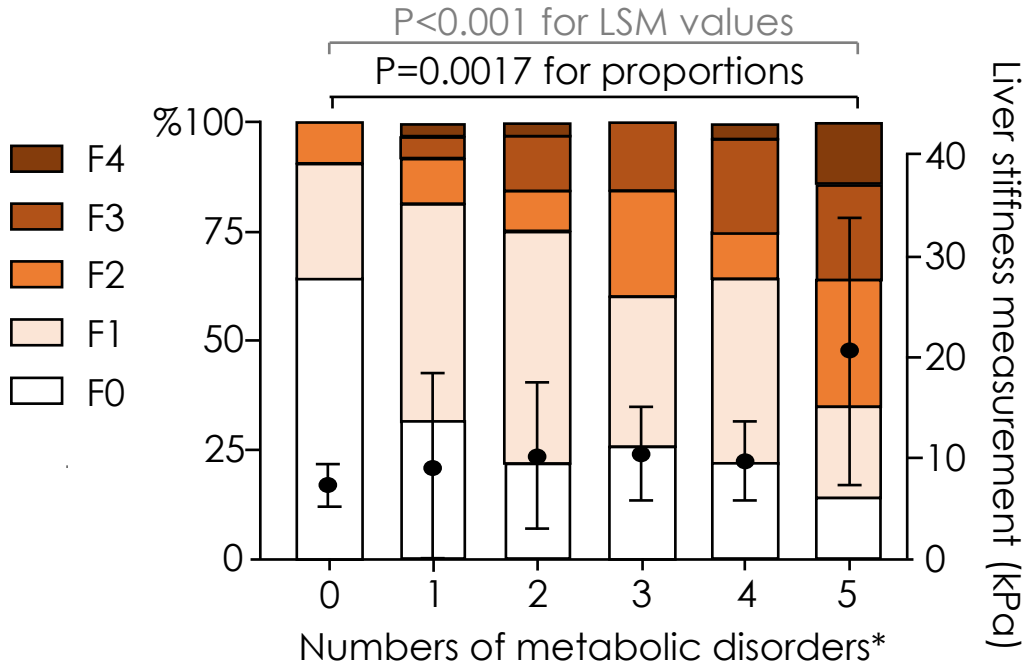
Association between metabolic disorders and liver fibrosis

A significantly higher proportion of patients with MetS had significant fibrosis (≥F2, **38% vs. 23%,** p=0.014) and higher LSM values (9.2 kPa, vs. 7.4 kPa, p=0.002) compared with patients without MetS

- Patients with more metabolic disorders had **more severe fibrosis** compared with patients with fewer metabolic disorders (p=0.017)

- Reduced **HDL-C** (OR 2.241, 95% CI 1.004;5.002, p=0.049) and raised **fasting glucose** (OR 4.500, 95% CI 2.083;9.725, p<0.001) were **significantly associated with advanced fibrosis**

Association between fibrosis stages, LSM and number of metabolic disorders



*Metabolic disorders referred to five components of metabolic disorders (IDF 2005): central obesity, raised blood pressure, reduced high-density lipoprotein cholesterol, raised triglyceride and raised fasting plasma glucose. CI, confidence interval; HDL-C, high density lipoprotein cholesterol; IDF, International Diabetes Federation; LSM, liver stiffness measurement; MetS, metabolic syndrome; NFS, NAFLD fibrosis score; OR, odds ratio.

Shi YW, et al. J Clin Transl Hepatol 2021; doi:10.14218/JCTH.2021.00058.

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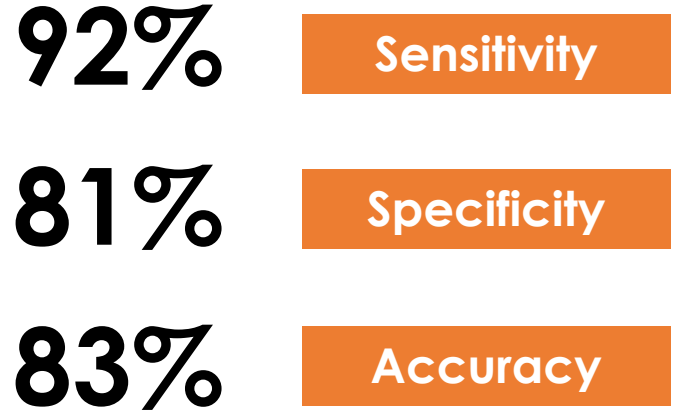
Metabolic disorders (MetDis) as a screening tool for advanced fibrosis

- A new diagnostic tool (MetDis) was developed using **reduced HDL-C** and **raised fasting glucose** to screen for advanced fibrosis
- By combining MetDis with the standard non-invasive test FIB-4, the number of **patients requiring liver biopsy was reduced** compared with FIB-4 alone (36% to 17%, $p<0.001$), due to the high negative predictive value of FIB-4 + MetDis

Sensitivity, specificity and accuracy of MetDis as a screening tool for advanced fibrosis



In this study population, metabolic disorders contributed to the severity of fibrosis in patients with NAFLD and should be taken into consideration during diagnosis and management of the disease. New combinations of metabolic disorders with non-invasive measurements provided a more accurate diagnosis for advanced fibrosis

HDL-C, high-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease.

Shi YW, et al. J Clin Transl Hepatol 2021; doi:10.14218/JCTH.2021.00058.

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A consensus-driven proposed nomenclature and new definition for MAFLD

- Due to the strong association between NAFLD and metabolic dysfunction, it has been proposed that the name '**metabolic associated fatty liver disease (MAFLD)**' is a more appropriate term for the disease[1]

- The change from NAFLD to MAFLD has been supported by international panels of experts, including the **Chinese Society of Hepatology** (CSH)[2]
  - **95.45%** of 66 leading hepatologists and gastroenterologists in China contacted by the CSH supported changing the nomenclature from NAFLD to MAFLD

- Some research suggests that the MAFLD criteria are **more effective** at identifying patients at risk of fibrosis and cardiometabolic complications compared with NAFLD[3,4]

- **However, these comparisons of the NAFLD and MAFLD terminology have been based in non-invasive indicators of fibrosis rather than comparing liver pathology and its relevance to MAFLD diagnostic criteria**

NAFLD, non-alcoholic fatty liver disease.

1. Eslam M, et al. J Hepatol 2020;73(1):202–209; 2. Nan Y, et al. J Hepatol 2021;75(2):454–461; 3. Lin S, et al. Lin Int 2020;40(9):2082–2089; 4. Yamamura S, et al. Liv Int 2020;40(12):3018–3030.

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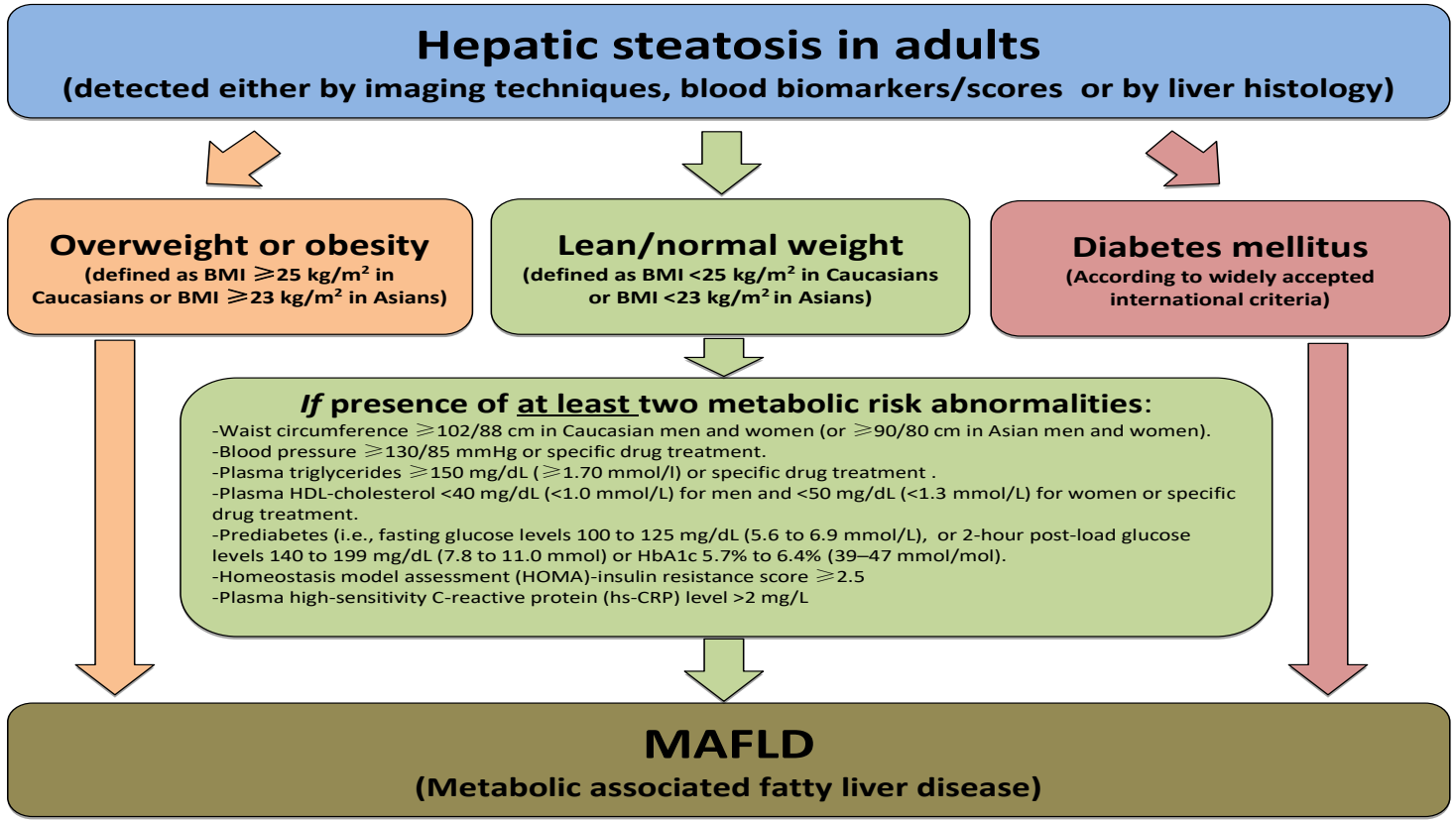
Proposed ‘positive’ diagnostic criteria for MAFLD



BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; MAFLD, metabolic associated fatty liver disease

1. Eslam M, et al. J Hepatol. 2020;73:202–9

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TOWARDS1 study

Metabolic Disorders Combined with Non-invasive Tests to Screen Advanced Fibrosis in NAFLD[1]

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MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

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Clinical characteristics of enrolled patients

150 patients (61%) with NAFLD met the diagnostic criteria of MetS*

- **56 patients (22.8%) had hypertension, 57 patients (23.2%) had dyslipidemia, 66 patients (26.8%) had T2D, and 6 patients (2.44%) had CVD**

- **Of the 246 patients enrolled, 39 (15.9%) were identified as having NAFL, 136 (55.3%) had early NASH, 65 (26.4%) had fibrotic NASH, and 6 (2.4%) were histologically defined as having NASH cirrhosis**

- **97.2% of patients met the metabolic criteria of MAFLD†**

*The diagnosis of MetS was based on the presence of more than three of the following metabolic risk factors according to the guidelines of prevention and treatment of NAFLD (2018, China): (1) abdominal obesity; (2) arterial hypertension; (3) hypertriglyceridemia; (4) low HDL-C; (5) hyperglycemia. †MAFLD was diagnosed by the criteria of histological hepatic steatosis in addition to one of the following: overweight/obesity (BMI ≥23 kg/m^2, Asian criteria), presence of T2DM, or evidence of metabolic dysregulation.
BMI, body mass index; CVD, cardiovascular disease; MAFLD, metabolic associated fatty liver disease; MetS, metabolic syndrome; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes.
Yang RX, et al. Hepatobiliary Pancreat Dis Int 2021; doi:10.1016/j.hbpd.2021.06.002.

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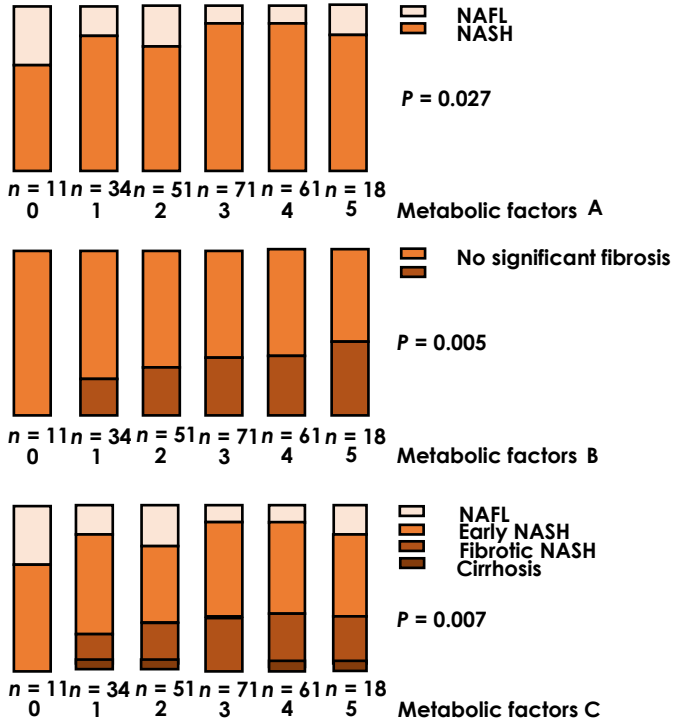
Association between MetS and severity of liver pathology

- Patients with MetS had higher histological scores of **lobular inflammation, ballooning** and **fibrosis** compared with patients without MetS
- The proportion of patients with **NASH**, **significant fibrosis** and **fibrotic NASH** were higher in the group of patients with MetS compared with those without MetS

Prevalence of NASH (A), significant fibrosis (B) and pathology stage (C) in patients with different numbers of metabolic components



MetS, metabolic syndrome; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis.
Yang RX, et al. Hepatobiliary Pancreat Dis Int 2021; doi:10.1016/j.hbpd.2021.06.002.

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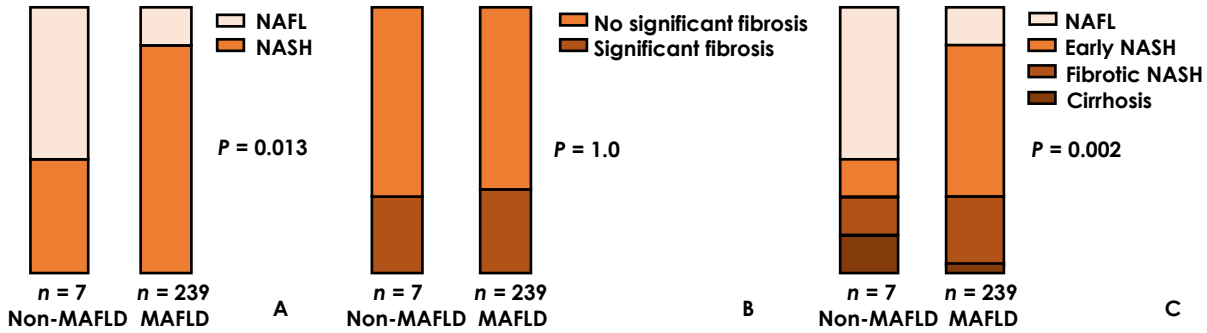
The diagnosis of MAFLD in the NAFLD population

- Of the 246 patients included in the study, 239 **(97.2%)** met the diagnostic criteria for **MAFLD**
- Fewer patients who did not meet the diagnostic criteria of MAFLD presented with **NASH (43.9% vs 86.4%)**
- The proportion of patients with significant **fibrosis** and **cirrhosis** was **similar** in both groups

Proportion of patients with NASH (A), significant fibrosis (B) and disease progression (C) in MAFLD and non-MAFLD groups



MAFLD, metabolic associated fatty liver disease; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
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MAFLD diagnostic criteria and liver histologic features

MAFLD patients with **BMI ≥ 23 kg/m²** had a greater percentage of **NASH** compared with patients with BMI <23 kg/m² (OR 2.975, 95% CI 1.037;8.538, P = 0.043)

- MAFLD patients with **T2D** had a greater risk of **significant fibrosis** (stage ≥F2) compared with patients without T2D, independent of BMI (OR 2.531, 95% CI 1.388;4.613, P = 0.002)

- **HOMA-IR ≥ 2.5** was the most significant risk factor for **NASH** (OR: 4.100; 95% CI: 1.772–9.487; P = 0.001) and **liver fibrosis** (OR: 2.947; 95% CI: 1.398–6.210; P = 0.004) adjusted for overweight and T2D

In this study population, the presence of MetS was associated with a greater severity of steatohepatitis and fibrosis. Furthermore, the results of the study indicate that the severity of insulin resistance may predict the progression of steatohepatitis and liver fibrosis.

BMI, body mass index; CI, confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance; MAFLD, metabolic associated fatty liver disease; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; T2D, type 2 diabetes.

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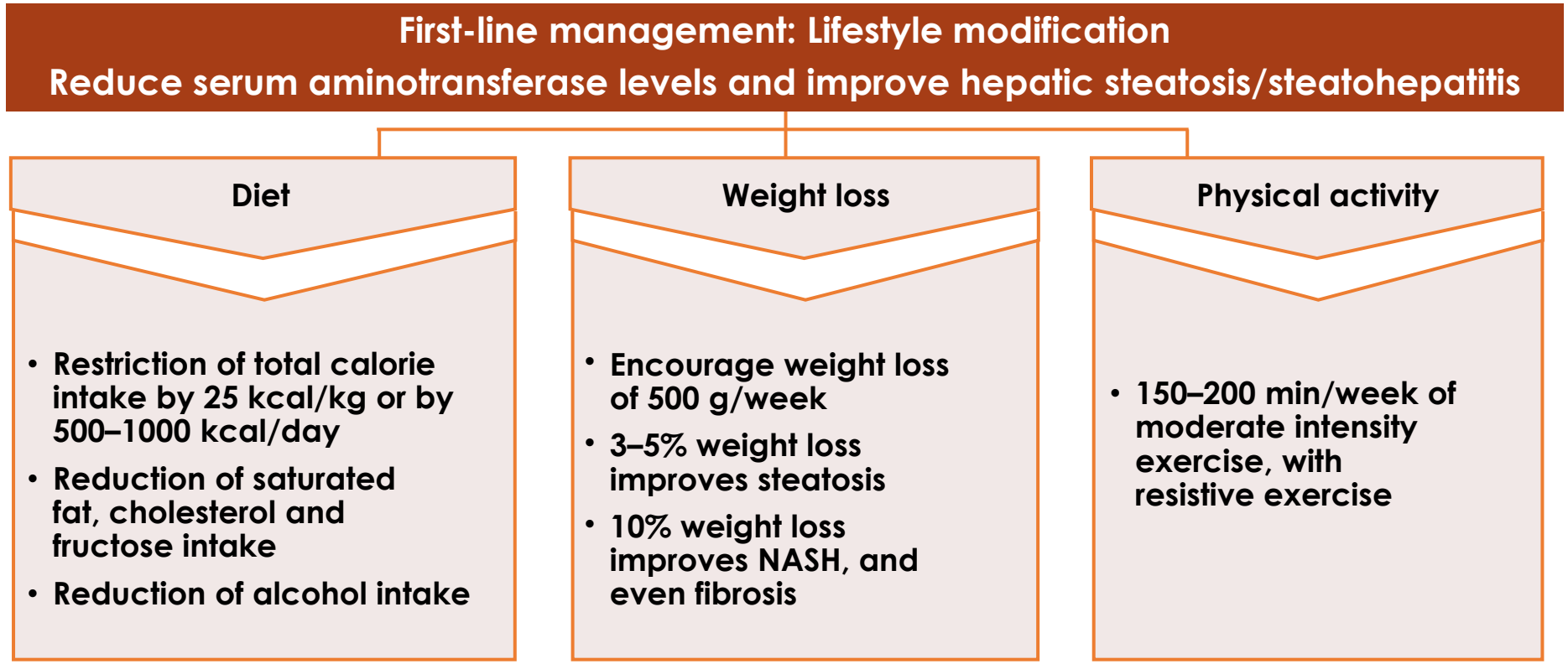
Chinese guidelines on the treatment of NAFLD[1,2]



NAFLD, non-alcoholic fatty liver disease; NASH, non-alcohilic steatohepatitis.

1. Gao X, et al. J Diabetes 2013;5:406–15; 2. Fan JG, et al. J Dig Dis. 2018;1–11.

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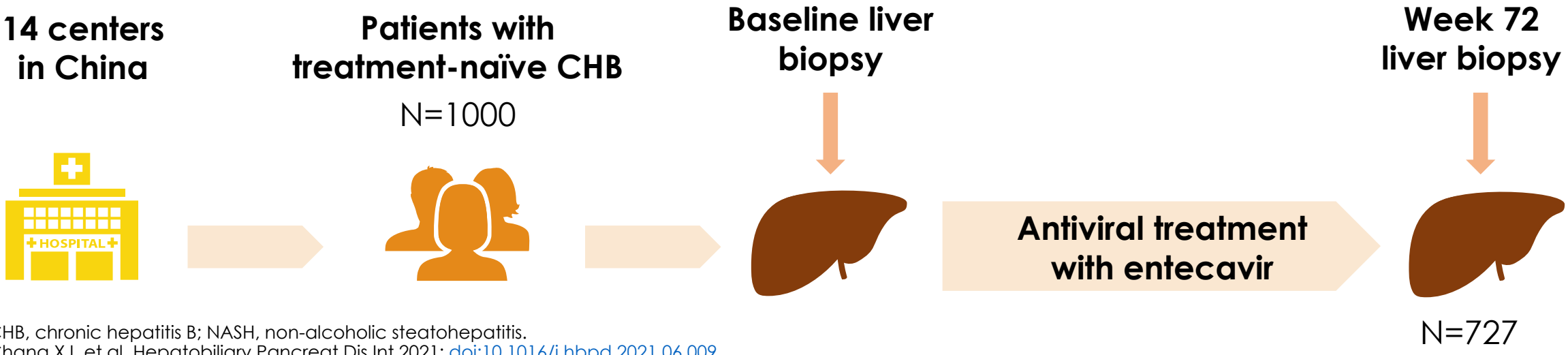
Steatohepatitis in patients with CHB during antiviral treatment
Role of weight management

- Prevalence of concomitant NASH was 18.2% in 1000 biopsy-proven patients with CHB
- **Factors influencing outcomes of NASH in patients with CHB receiving antiviral treatment** were investigated in a ***post-hoc* analysis** of a multicenter trial (NCT01965418)



CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis.
Chang XJ, et al. Hepatobiliary Pancreat Dis Int 2021; doi:10.1016/j.hbpd.2021.06.009.

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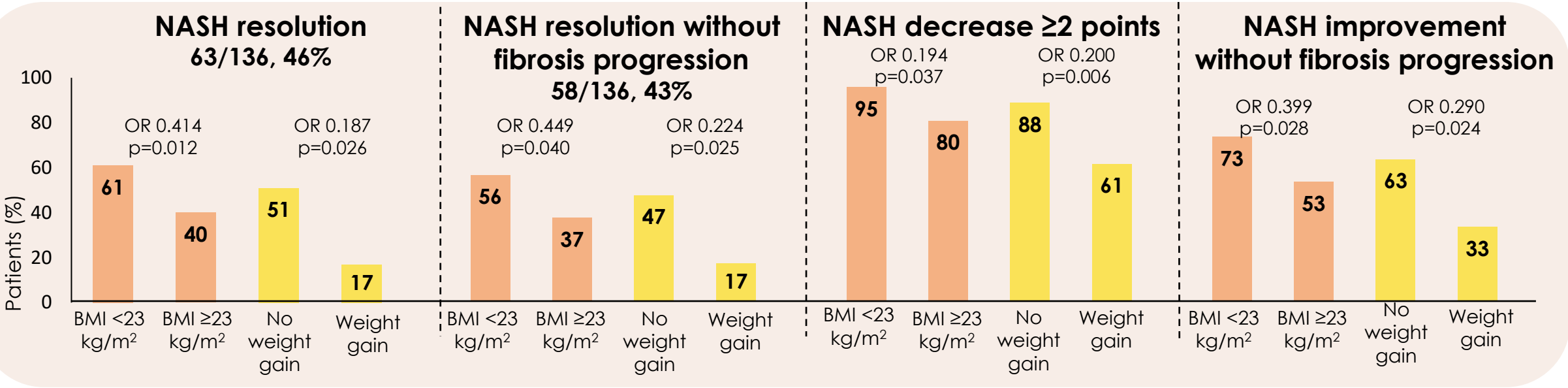
Impact of baseline BMI and weight gain on improvement of NASH in patients with CHB during antiviral treatment



Among CHB patients with NASH, baseline overweight and subtle weight gain during follow-up were less likely to experience improvement or resolution of NASH. Virological outcomes did not have an impact on resolution of NASH

BMI, body mass index; CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis; OR, odds ratio.
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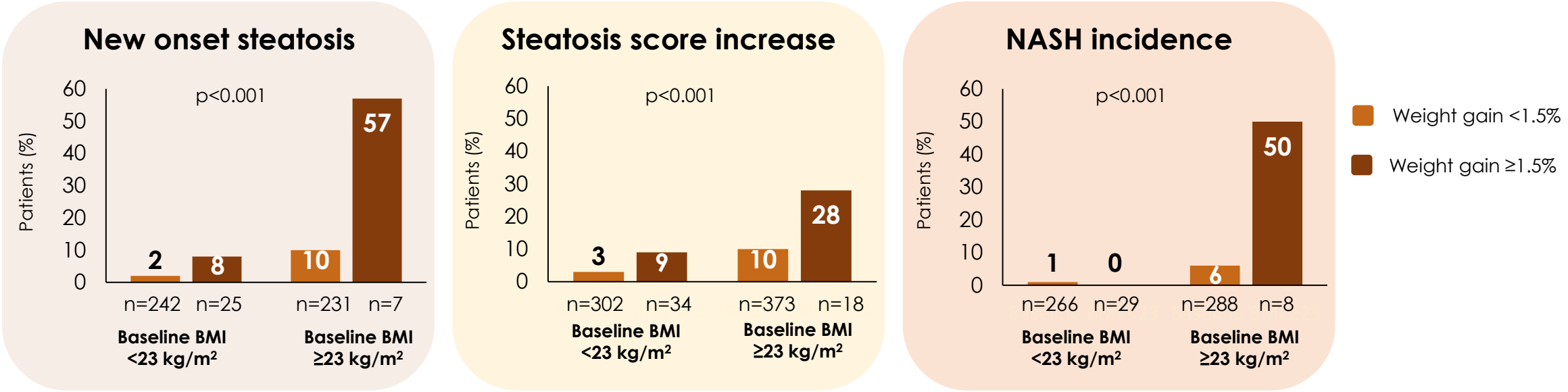
Impact of baseline BMI on incidence of NASH and steatosis in patients with CHB during antiviral treatment



Among patients without NASH at baseline, 22 (3.7%) developed NASH. Baseline overweight (OR: 12.506; 95% CI: 2.813-55.606; P = 0.001) and subtle weight gain (OR: 5.126; 95% CI: 1.674-15.694; P = 0.005) were predictors of incident NASH.

BMI, body mass index; CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis.
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Chinese guidelines on the treatment of NAFLD

Pharmacotherapy[1]

	NAFLD	NASH
Metformin	To improve insulin resistance and glucose metabolism (not liver-specific)	
Pioglitazone	To improve glucose metabolism (beneficial for liver with some side effects)	
Statin/Fibrates	To improve lipid metabolism and atherosclerosis/reduction of serum TG (not liver-specific)	
Angiotensin-2 receptor antagonist	To reduce arterial hypertension (not liver-specific)	
Orlistat	If weight reduction of >5% is not achieved with lifestyle modifications	

Hepatoprotectors[1,2]

- The use of 1–2 types of the following **hepatoprotective agents** is optional as adjunct therapy in NAFLD patients with biopsy-proven **NASH**, abnormal liver enzymes, or signs of **significant fibrosis**:
  - Polyene phosphatidylcholine
  - Vitamin E
  - Silymarin
  - Adenosylmethionine
  - Reduced glutathione

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TG, triglyceride.

1. Gao X, et al. Journal of Diabetes 2013;5:406–15; 2. Fan JG, et al. J Dig Dis 2018;1–11.

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Narrative literature review of polyene phosphatidylcholine[1]

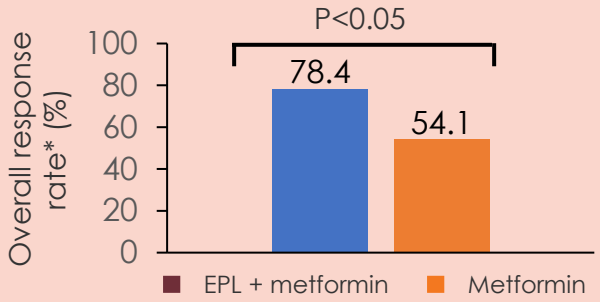
Efficacy of EPLs in patients with NAFLD and cardiometabolic comorbidities

NAFLD and T2DM

Six studies included patients with NAFLD and T2DM

EPLs given as **adjunctive therapy** to **metformin** or **SOC** in patients with NAFLD and T2DM are associated with **improved clinical outcomes** compared with T2DM-specific treatment alone[1–3]

In one study of patients with NAFLD and T2DM:[2]



NAFLD and hyperlipidemia or obesity

Four studies included patients with NAFLD and hyperlipidemia or obesity

EPL therapy resulted in i**mprovements in clinical outcomes** for patients with NAFLD and hyperlipidemia or obesity[4–6]

In one study of patients with NAFLD and obesity:[7]

PPC + sibutramine
- Significant reduction in steatosis from baseline†
- Significant improvement in ultrasound results in 92% of patients from baseline†

Sibutramine
- Significant increase in steatosis from baseline†
- No change in ultrasound results in 23.3% of patients from baseline

PPC + sibutramine resulted in slower fibrosis progression than sibutramine alone, p<0.05

*Overall response rate was defined as symptoms and physical signs show improvement; liver ultrasonic appearance shows that fatty liver improves or decreases. †p<0.05.
EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; SOC, standard of care; PPC, polyene phosphatidylcholine; T2DM, type 2 diabetes mellitus. Slide refers to EPL products containing high amounts of PPC.

1. Dajani A, et al. Drugs Ther Perspect 2020;37:249–64; 2. Li Z. Inner Mongol Journal of Traditional Chinese Medicine 2013;31:10–1; 3. Sun C et al. Clinical Focus 2008;23:1272–3; 4. Wu CY. Pract Clin Med 2015;16:3–5; 5. Maev IV, et al. BMJ Open Gastroenterol 2019;6:e000307; 6. Maev IV, et al. BMJ Open Gastroenterol 2020;7:e000368; 7. Maev IV, et al. BMJ Open Gastroenterol 2020;7:e000341; 8. Sas E et al. Gut 2012;61:A216–A7

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Are you aware of the impact of NAFLD/MAFLD on clinical outcomes in patients with COVID-19?

1. Yes
2. No

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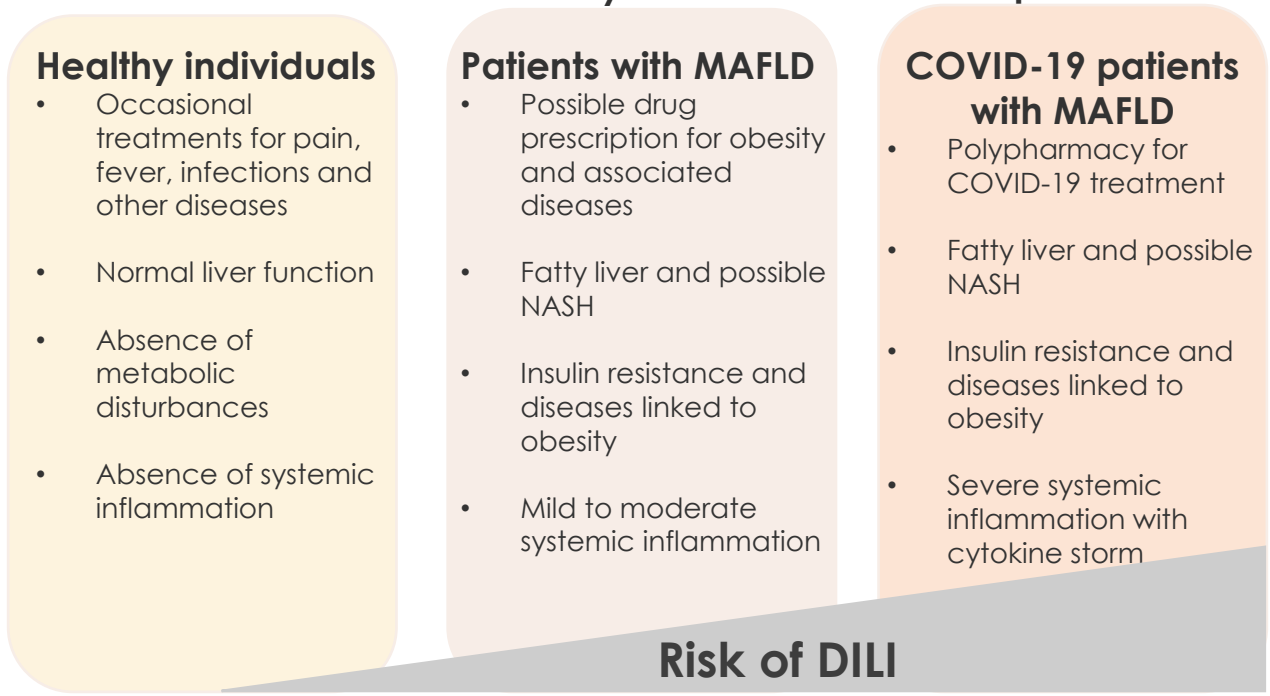
NAFLD and COVID-19

- NAFLD/MAFLD patients often present with **elevated cytokine** levels, making them more vulnerable to **exaggerated cytokine production associated with COVID-19**[1]

- **NAFLD/NASH is a significant risk factor for hospitalization** for COVID-19, and appears to account for risk attributed to obesity[2]

- Patients with NAFLD/NASH often have components of **MetS** such as hypertension, obesity, and diabetes that put them at higher risk of **severe COVID-19 disease**. Patients with COVID-19 and NAFLD are at increased risk of COVID-19 **disease progression, abnormal liver function, and longer period of viral shedding** in comparison with non-NAFLD individuals[3]

Obese patients with MAFLD and COVID-19 have higher risk for DILI than non-infected healthy individuals or MAFLD patients[5,6]



The observations that MAFLD patients have almost double the risk of the general population to progress severe COVID-19.[4] MAFLD is associated with 4–6-fold increase in severity of COVID-19 compared to non-MAFLD patients.

COVID-19, disease caused by coronavirus; DILI, drug-induced liver injury; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

1. M.I. Metawea, W.I. Yousif and I. Moheb / Digestive and Liver Disease 2020;14:32.2. Bramente C et al. medRxiv 2020; doi 10.1101/2020.09.01.20185850; 3. Rezasoltani S, et al. Front Med 2020;7:398; 4. Paola Dongiovanni et al. Expert Rev Gastroenterol Hepatol 2020;14:867–872; 5. Ferron PJ et al. Biochimie 2020;179:246–74. 6.Tao Z et al. J Clin Gastroenterol 2021;55:830–35.

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Conclusions

1. Combining MetDis with FIB-4 provided an accurate, non-invasive method for diagnosis of advanced fibrosis in the TOWARDS1 study
2. In the TOWARDS1 study, the presence of MetS was associated with a greater severity of steatohepatitis and liver fibrosis in patients with NAFLD
3. Insulin resistance status may play a more predominant role in the progression of MAFLD than obesity and history of diabetes
4. The Chinese Guidelines recommend lifestyle modifications as first-line treatment for NAFLD, followed by medications to improve insulin resistance and metabolic status, and hepatoprotective agents for steatohepatitis and fibrosis

MAFLD, metabolic associated fatty liver disease; MetDis, metabolic disorders; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease.

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Shanghai Jiao Tong University School of Medicine

THANKS!