Understanding the risk of and risk factors associated with progression to advanced liver disease in patients with NAFLD

Vincent Wong
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Disclosures

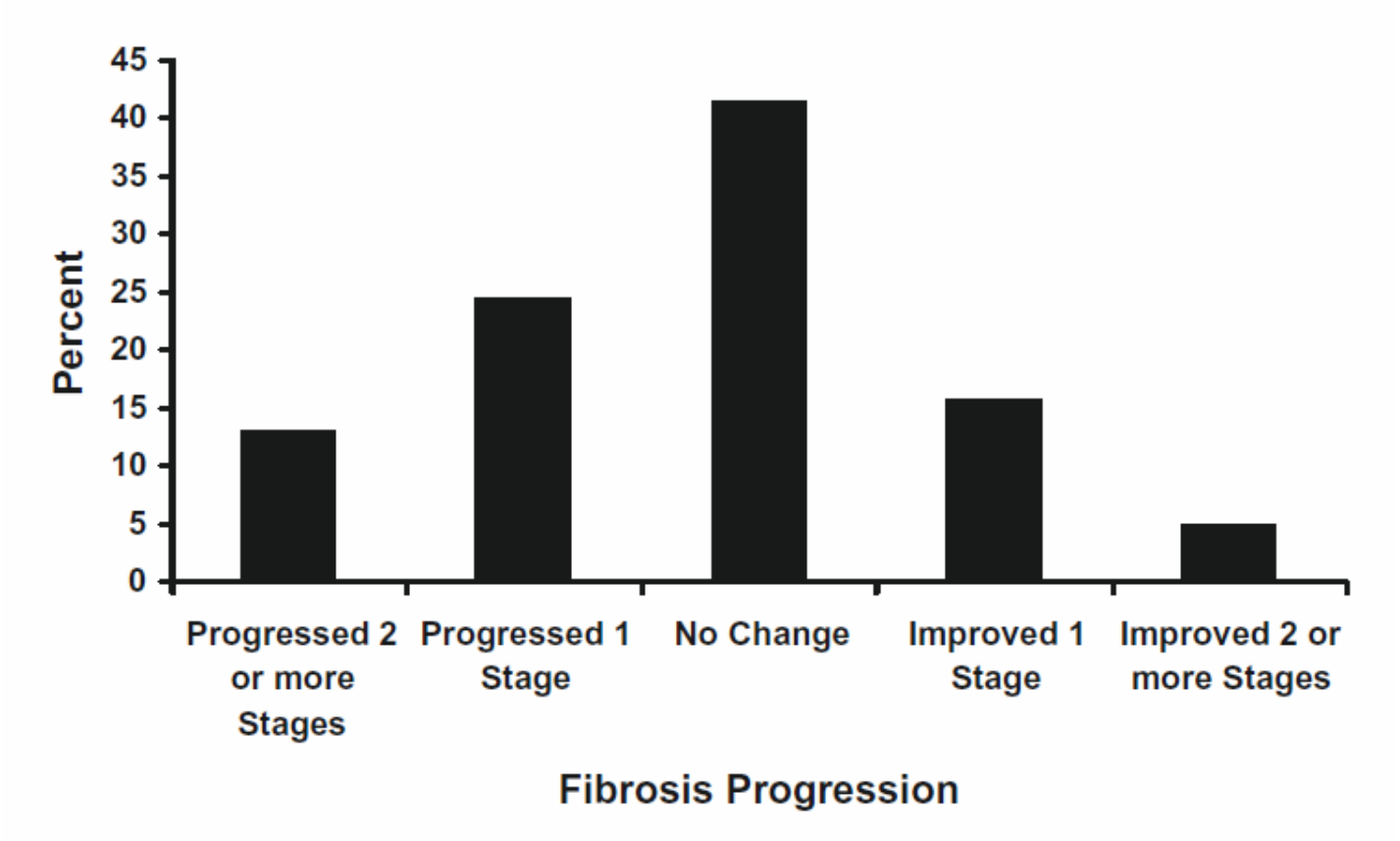
- Consultancy: 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Hanmi Pharmaceutical, Intercept, Merck, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, ProSciento, Sagimet Biosciences, TARGET-NASH, Terns
- Lectures: AbbVie, Bristol-Myers Squibb, Echosens, Gilead Sciences
- Research grants: Gilead Sciences

How do we assess disease progression?

Study design	Advantages	Disadvantages
Paired liver biopsies in routine settings	- Histological data	- Selection bias: More severe patients
Paired liver biopsies in clinical trials	- Histological data - High quality clinical data	- Selection bias: More severe patients; narrow spectrum - Intervals usually too short
Serial non-invasive tests	- Can capture a broader spectrum of patients	- Test accuracy - Responsiveness of most tests poorly defined

Fibrosis progression in NASH

Systematic review of 10 studies comprising 221 patients



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Argo et al. J Hepatol 2009;51:371

Prospective 3-year liver biopsy in unselected NAFLD patients

NAFLD activity score at month 36	<3	3–4	≥5	Total
NAFLD activity score at baseline				
<3	12	16	1	29
3–4	5	10	3	18
≥5	0	5	0	5
Total	17	31	4	52

Month 36	F0	F1	F2	F3	F4	Total
Baseline						
F0	17	7	0	1	1	26
F1	7	7	1	2	0	17
F2	4	1	0	1	1	7
F3	0	0	1	0	0	1
F4	0	0	0	0	1	1
Total	28	15	2	4	3	52

- It is possible to progress from NAFL to NASH or have regression of NASH
- Around 25% patients had fibrosis progression in 3 years
- Fibrosis progression can occur in NAFL patients
- A minority of patients may have fast fibrosis progression

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Wong VW et al. Gut 2010;59:969

Evidence of progression from NAFL to NASH in a UK cohort

Baseline disease activity	Follow-up disease activity			
	Bland steatosis	Steatosis and mild inflammation	NASH	Total
Bland steatosis	7	**6**	**4**	17
Steatosis and mild inflammation	2	0	**8**	10
NASH	5	1	75	81
Total	14	7	87	108

Numbers in **bold** indicate progression of disease activity.

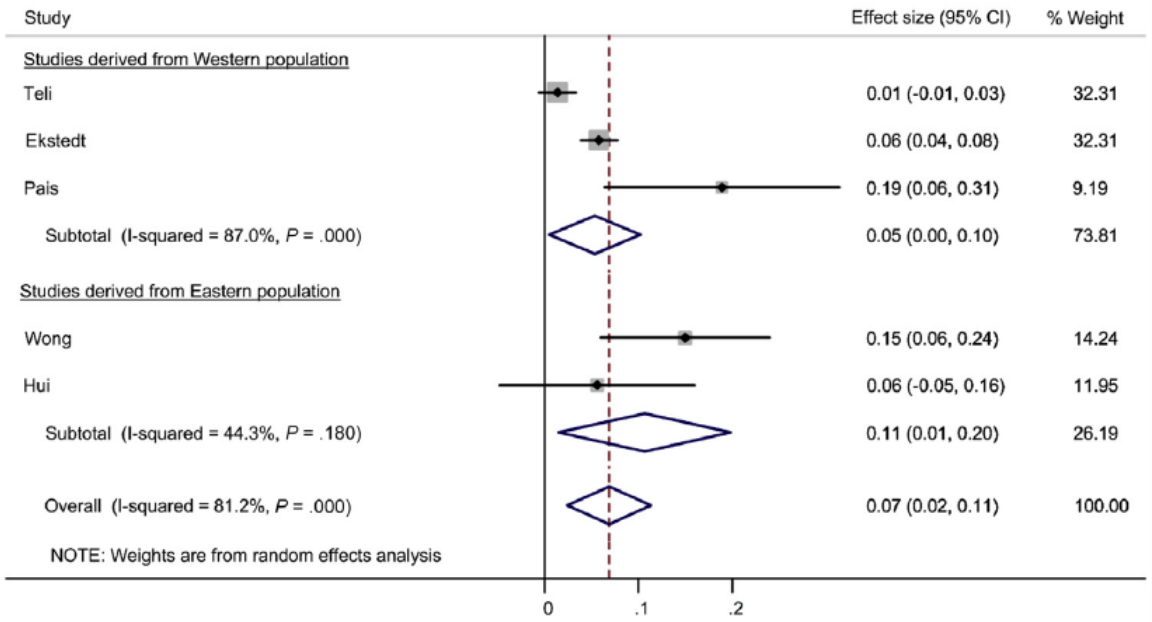
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

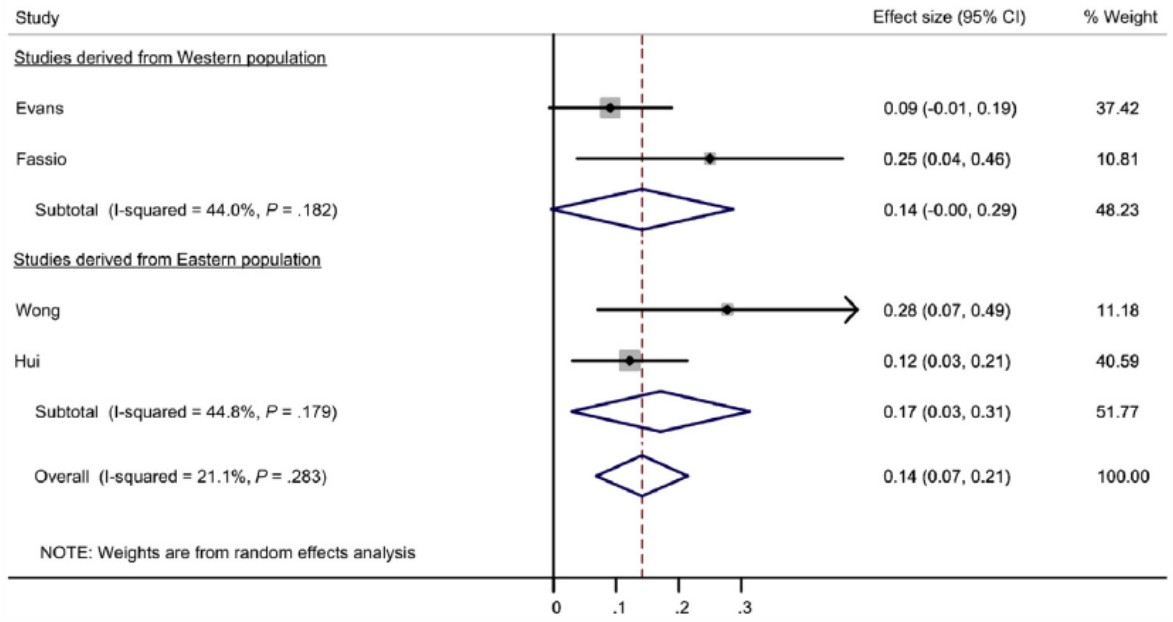
McPherson et al. J Hepatol 2015;62:1148

Fibrosis progression rate in NAFL and NASH

NAFL
Fibrosis progression = 7% per year
= 1 stage in 14 years

NASH
Fibrosis progression = 14% per year =
1 stage in 7 years





香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Singh et al. Clin Gastroenterol Hepatol 2015;13:643

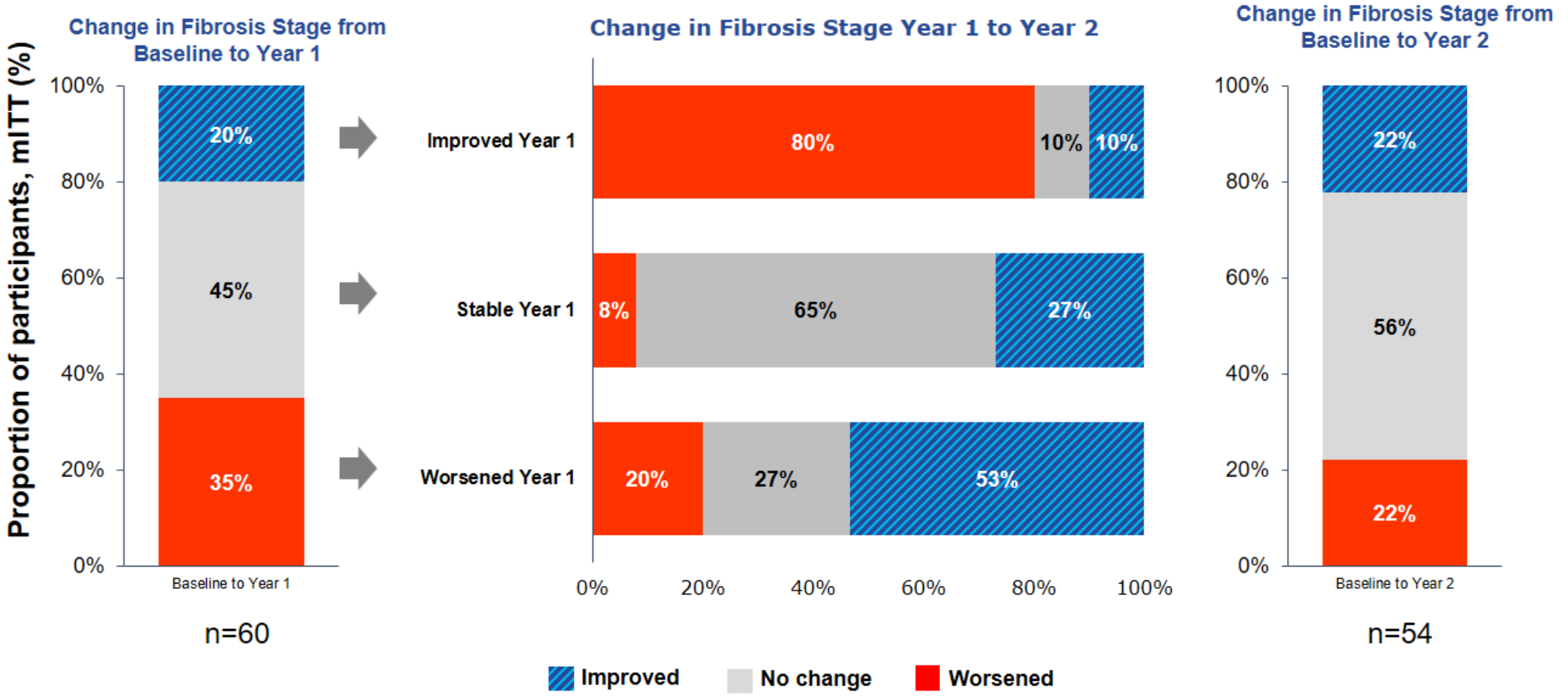
Summary of fibrosis progression in the placebo arms of NASH trials

Study	Study drug	Baseline fibrosis stage	N in placebo arm	Interval between biopsies	Fibrosis change
Harrison 2018	Simtuzumab	F3-4	69 (F3)	2 years	23% improved 22% worsened
Younossi 2019	Obeticholic acid	F1-3	220	1.5 years	23% improved 21% worsened
Ratziu 2020	Cenicriviroc	F1-3	54	2 years	22% improved 22% worsened
Harrison 2020	Selonsertib	F3-4	159 (F3)	1 year	16% improved 16% worsened

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Harrison et al. Gastroenterology 2018;155:1140, Younossi et al. Lancet 2019;394:2184,
Ratziu et al. Hepatology 2020 [Epub ahead of print], Harrison et al. J Hepatol 2020 [Epub ahead of print]

“Seesaw” effect: substantial variability in fibrosis stage in placebo group of cenicriviroc trial

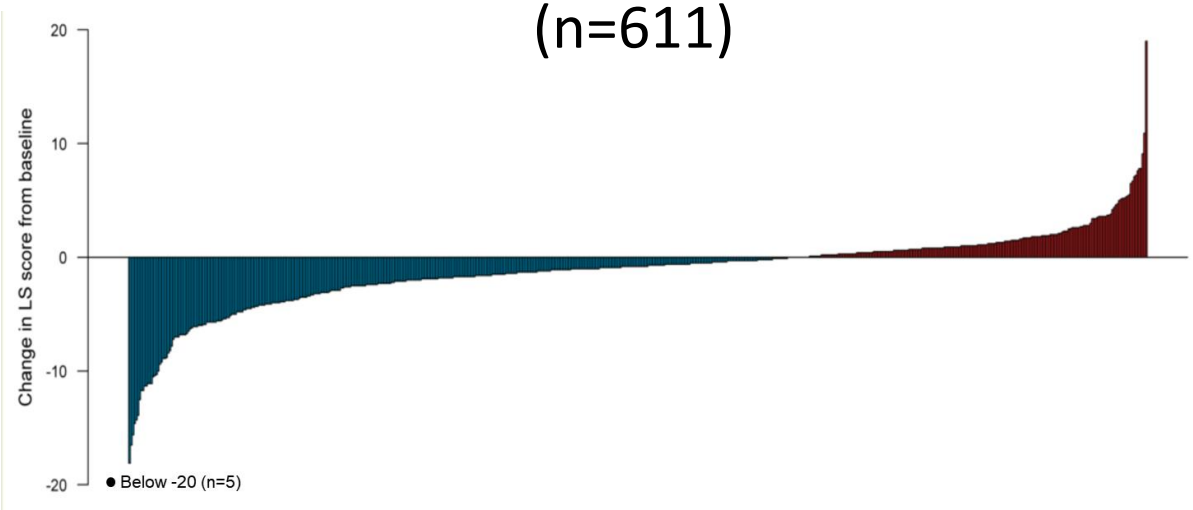


香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Ratziu et al. Hepatology 2020 [Epub ahead of print]

Monitoring patients with type 2 diabetes with transient elastography at 3 years

Change in liver stiffness in 3 years (n=611)



- 73/611 (12%) had ≥30% relative increase in LSM
- 21/487 (4%) had LSM increasing from <10 to ≥10 kPa

- 70/124 (56%) had LSM decreasing from ≥10 to <10 kPa

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Kwok et al. Gut 2016;65:1359, Lee et al. Hepatology 2020 [Epub ahead of print]

Use of non-invasive tests to study fibrosis progression

Non-invasive tests	Potential caveats
Liver stiffness measurement	- False-positive diagnosis of advanced fibrosis due to technical issues and confounding factors (e.g. active hepatitis, biliary obstruction, hepatic congestion, food intake, obesity and/or steatosis)
Simple fibrosis scores (e.g. APRI, FIB-4, NAFLD fibrosis score)	- Poor performance in extremes of age - Some parameters confounded by comorbidities - Age would go up with time regardless of disease progression - Some factors are largely irreversible (e.g. diabetes)
Specific biomarkers (e.g. ELF, Pro-C3)	- Some parameters confounded by comorbidities - Need longitudinal data

Fu et al. J Gastroenterol 2020 [Epub ahead of print]

Factors associated with fibrosis progression

Study	Study design	Factors associated with fibrosis progression
Wong 2010	Paired liver biopsies	ΔBMI, ΔWaist circumference, LDL-cholesterol
McPherson 2015	Paired liver biopsies	Platelet count, type 2 diabetes, GGT, NASH, fibrosis scores
Sanyal 2019	Simtuzumab trial	Hepatic collagen content and α-SMA, fibrosis scores
Lanthier 2019	Cenicriviroc trial	Hepatic collagen content and α-SMA, serum TGF-β and TIMP-1
Lee 2020	Paired transient elastography	BMI, ALT, ΔALT

Factors:

1. Metabolic risk factors of disease progression
2. Disease activity
3. Markers of more severe disease severity at baseline

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Wong VW et al. Gut 2010;59:969, McPherson et al. J Hepatol 2015;62:1148, Sanyal et al. Hepatology 2019;70:1913, Lanthier et al. EASL 2019, Lee et al. Hepatology 2020 [Epub ahead of print]

Take home messages

- “We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten.” – Bill Gates
- “Rule of progression in 20%”
  - Partly real
  - Partly due to the inclusion of patients closer to the next stage
  - Partly due to variability in assessment tools
  - Important to know when designing clinical trials nonetheless
- Metabolic factors remain the most important risk factors of disease progression

Thank you very much!

State Key Laboratory of Digestive Disease
- Prof Henry Chan
- Prof Grace Wong
- Angel Chim
- Carmen Chan
- Sally Shu
- Julie Leung
- Ada Tse
- Pete Tse
- Katherine Kwan
- Sophia Lam

Department of Anatomical and Cellular Pathology
- Dr Paul Choi, Prof Anthony Chan

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Department of Imaging and Interventional Radiology
- Prof Winnie Chu

Shanghai Jiao Tong University Xinhua Hospital
- Prof Jian-Gao Fan

Australian National University
- Prof Geoff Farrell, Prof Shiv Chitturi

University of Sydney
- Prof Jacob George, Dr Mohammed Eslam

University of Malaya
- Prof W K Chan

University of Bordeaux
- Prof Victor de Lédinghen

Vincent Wong
wongv@cuhk.edu.hk