LEAD
LIVER EXPERTS FOR ADVANCING LIVER DISEASE DIAGNOSIS AND MANAGEMENT

HKASLD

香港肝癌及腸胃癌基金會
HONG KONG LIVER CANCER AND GASTROINTESTINAL CANCER FOUNDATION

CU Medicine HONG KONG
香港中文大學醫學院
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Liver Cancer Surveillance: From Local Consensus to Informing Regional Policies

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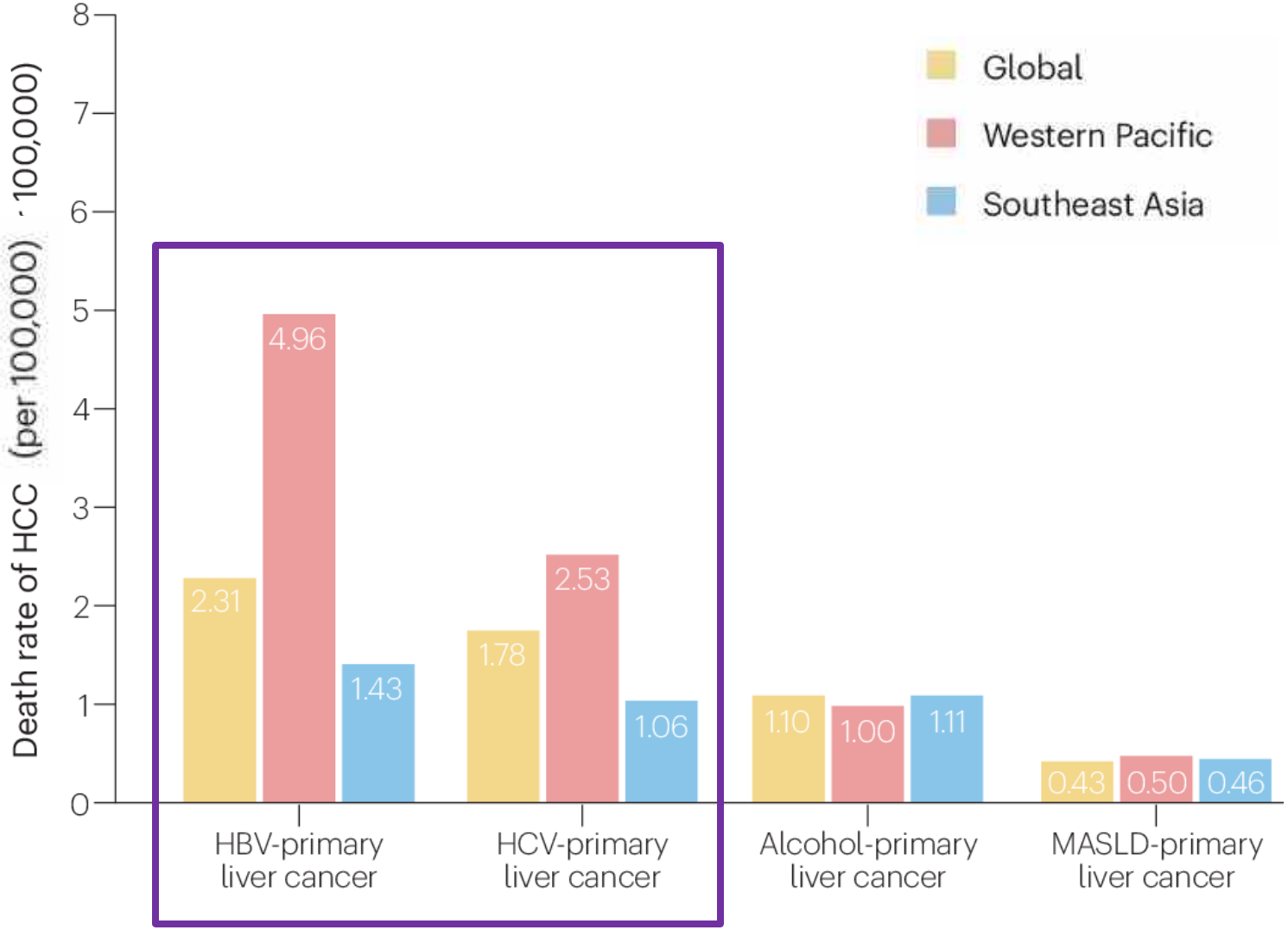
𝕏 @RashidLui

Overview

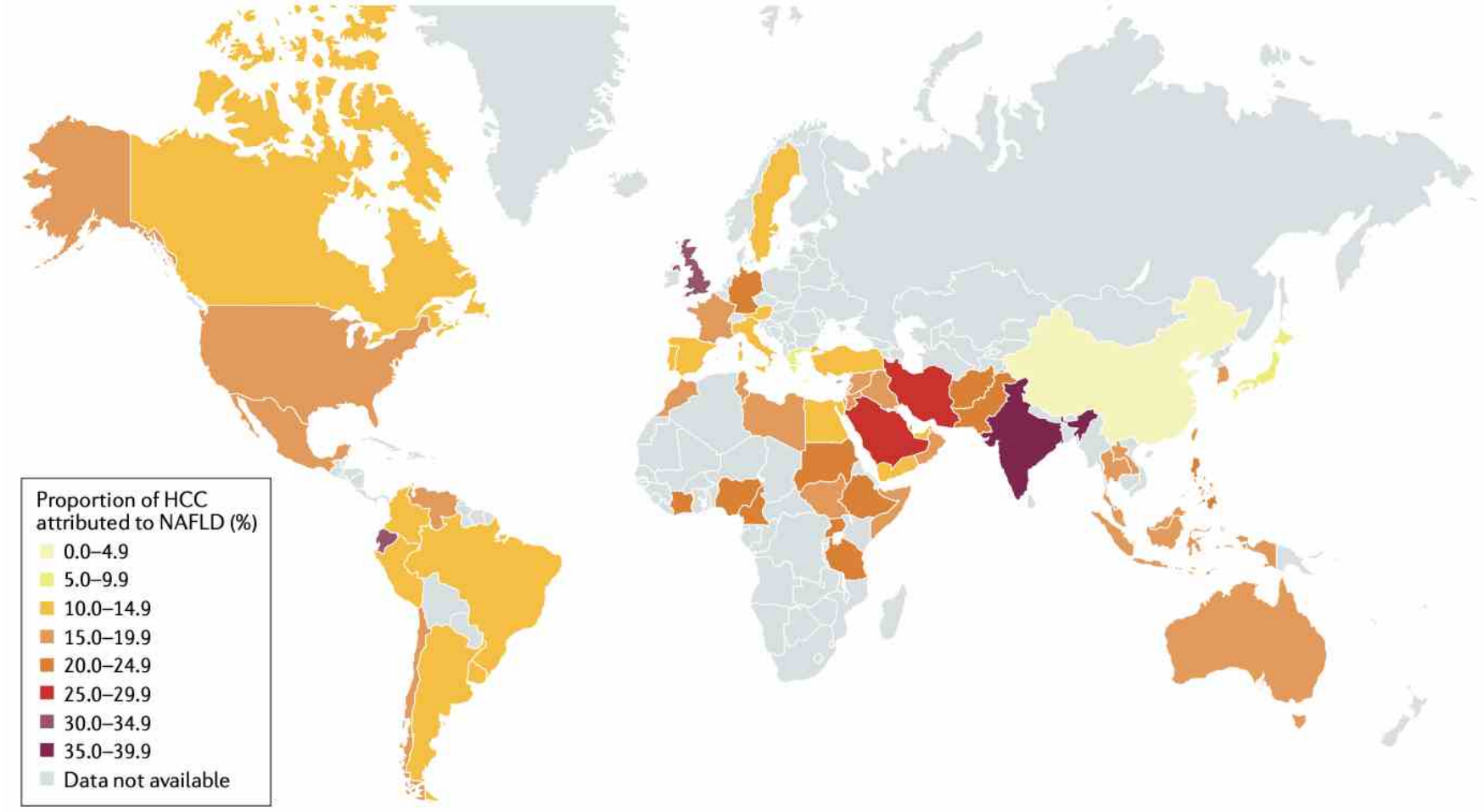
- **Background**
- Local hepatocellular carcinoma (HCC) surveillance recommendations
- Health economics
- HCC surveillance programmes in the Asia-Pacific

Death rates of HCC by aetiology and region in 2019



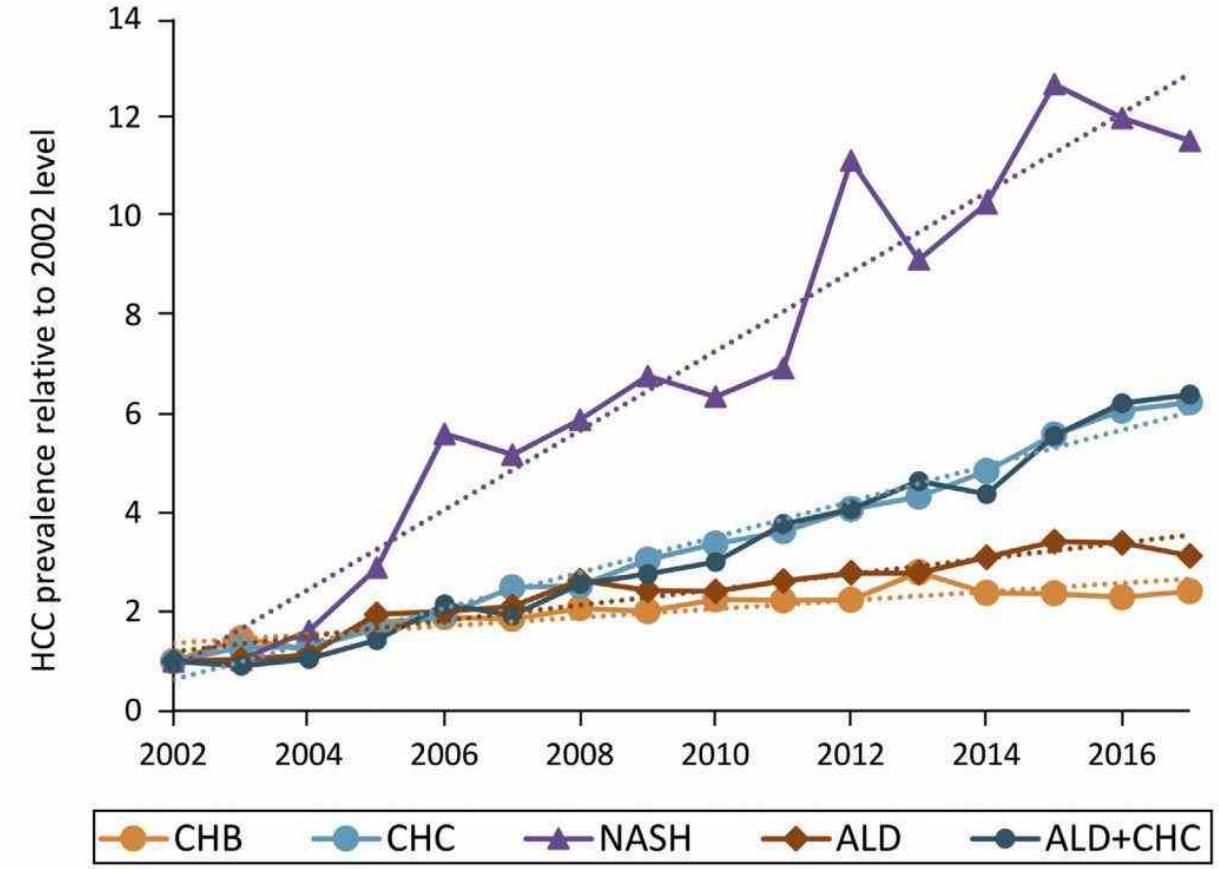
Adapted from Mak LY … Lui R et al. Nat Rev Gastroenterol Hepatol. 2024 Aug 15.

Proportion of HCC attributable to metabolic dysfunction-associated steatotic liver disease (MASLD)



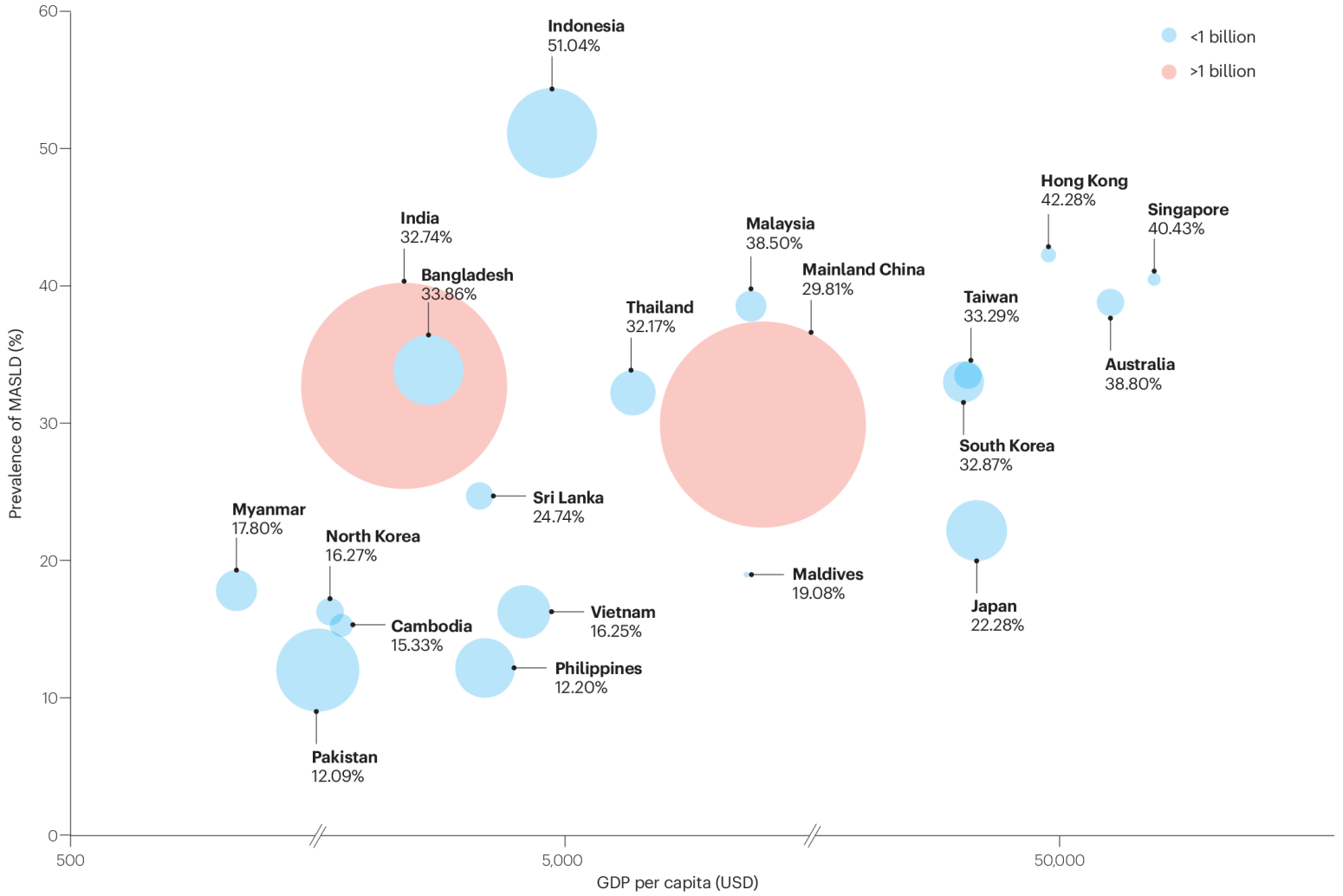
Huang, El-Serag and Loomba. Nat Rev Gastroenterol Hepatol. 2021 Apr;18(4):223-238.

Metabolic dysfunction-associated steatohepatitis (MASH) is the fastest growing cause of HCC in liver transplant candidates in the United States



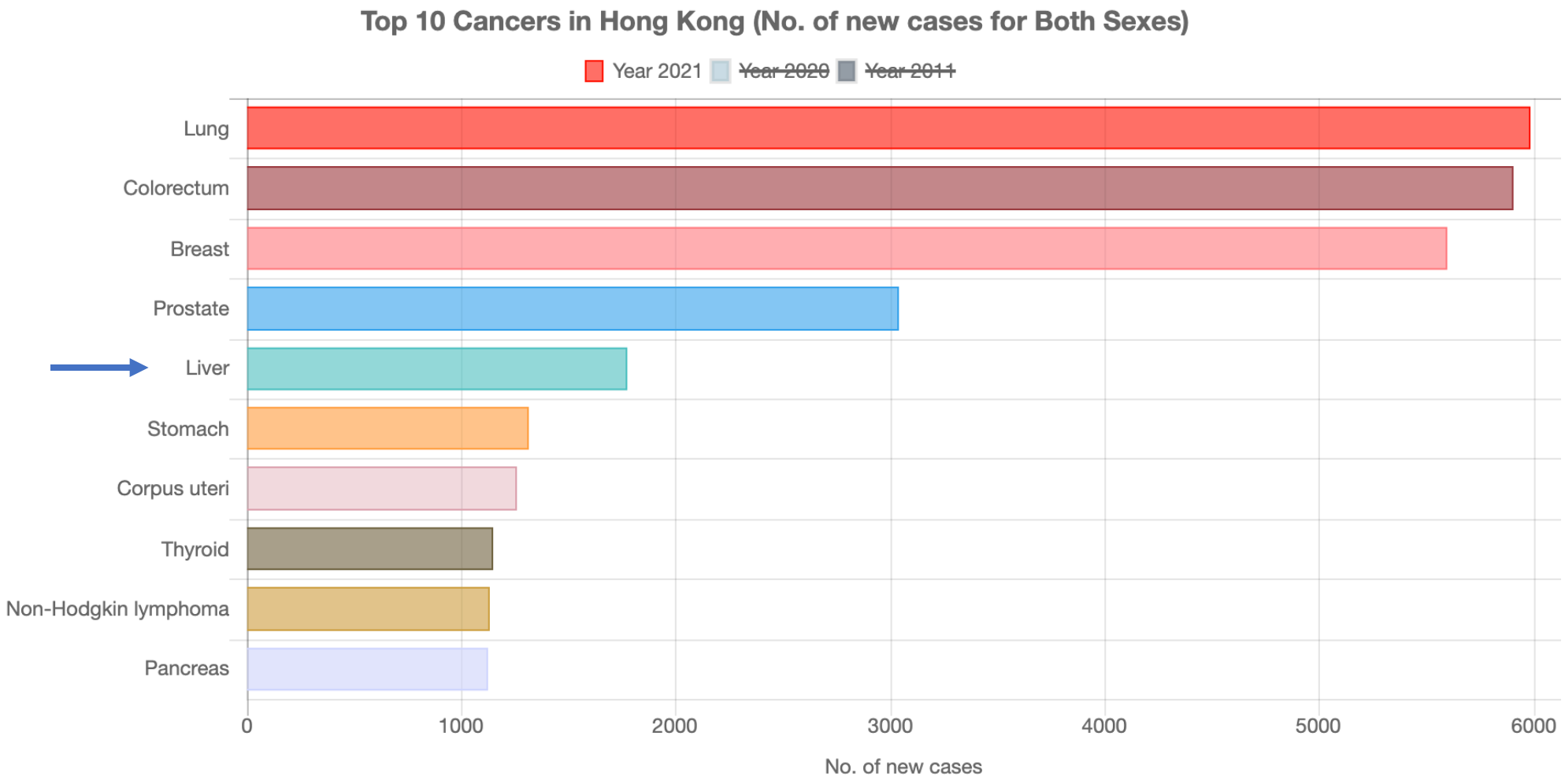
Younossi Z et al. Clin Gastroenterol Hepatol. 2019 Mar;17(4):748-755.e3.

MASLD prevalence in the Asia-Pacific (APAC)



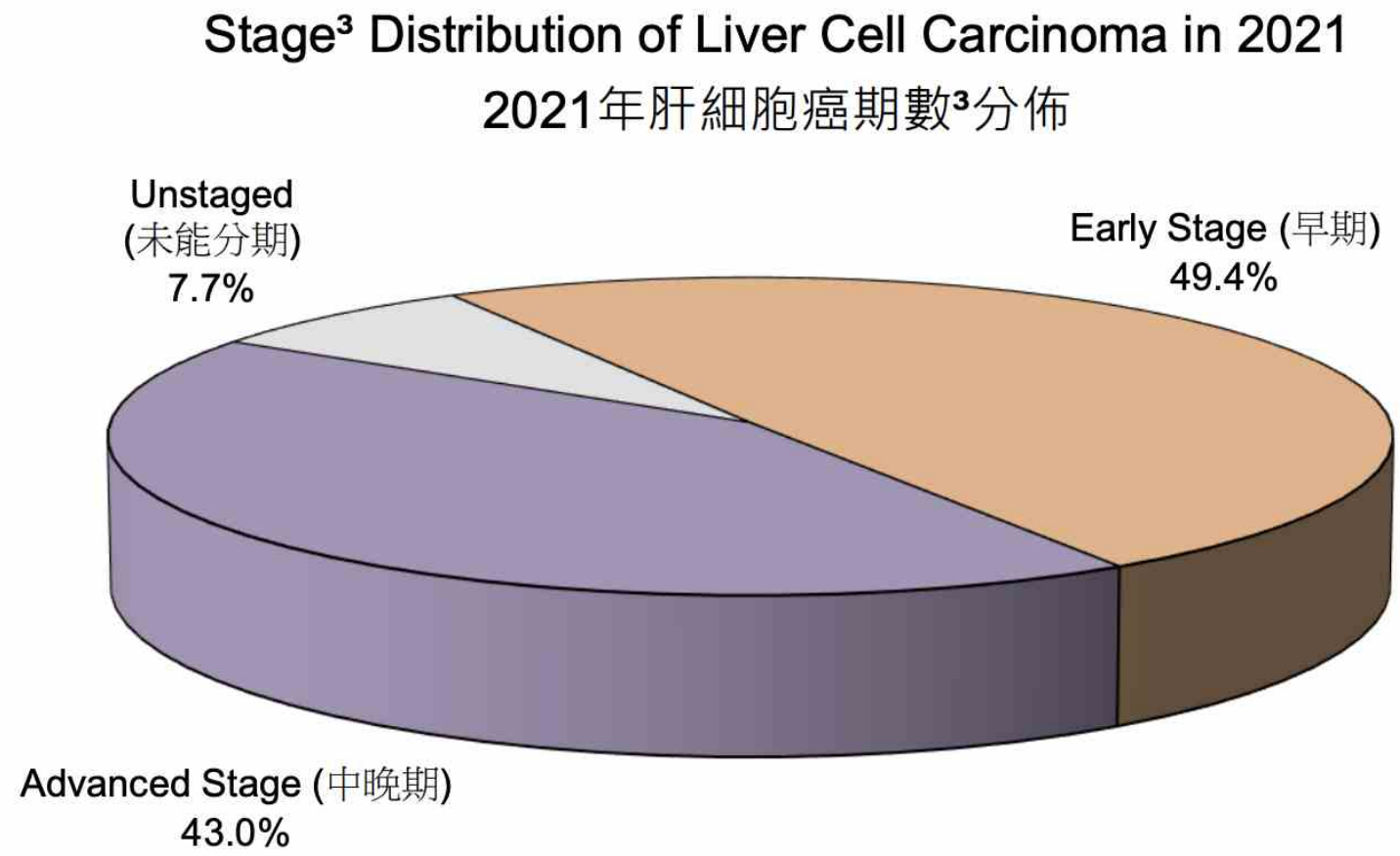
Mak LY … Lui R et al. Nat Rev Gastroenterol Hepatol. 2024 Aug 15.

HCC is the 5th most common cancer in Hong Kong



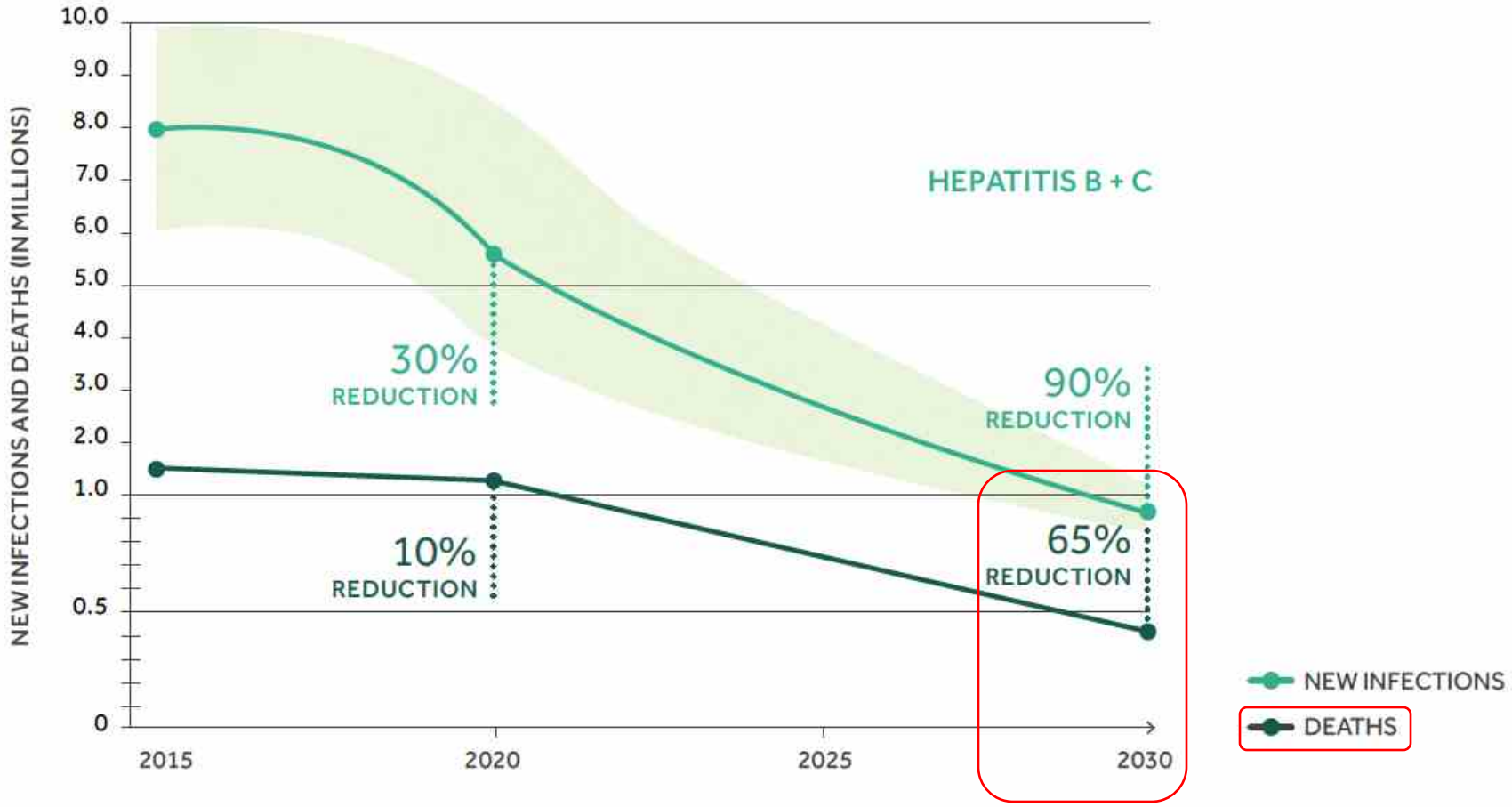
Source: Hong Kong Cancer Registry 2021

Stage distribution of HCC in Hong Kong



Source: Hong Kong Cancer Registry 2021

World Health Organization (WHO) targets for reducing new cases and deaths from chronic viral hepatitis



Majority of deaths are related to HCC

WHO 2016. Combating hepatitis B and C to reach elimination by 2030 - Advocacy brief

Hepatitis B & C in Hong Kong

HBV & HCV are the major causes of chronic liver disease, liver cirrhosis and liver cancer

100%
Blood donation from voluntary non-remunerated donors

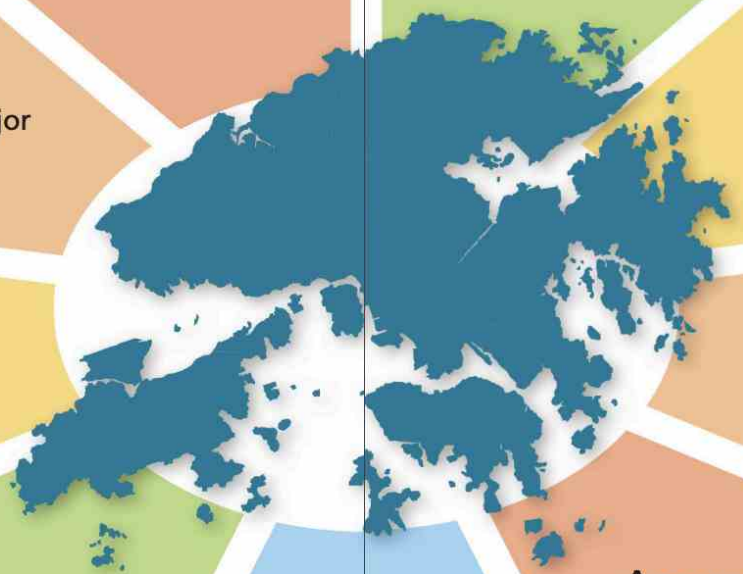
Nucleic acid testing of HBV and HCV

HBV:
Mother-to-child transmission is the major route of transmission

Universal neonatal hepatitis B vaccination was launched in 1988

HCV:
Injecting drugs is the major route of transmission

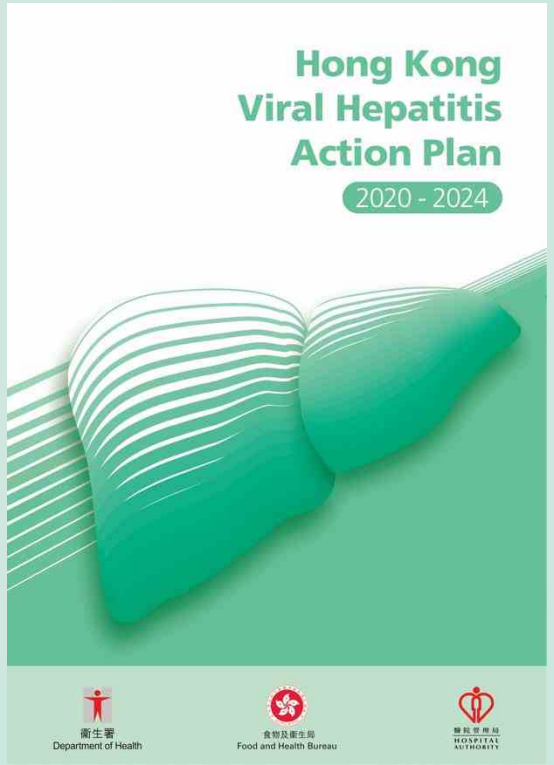
In 2018, 4.5%
antenatal women were found to be infected with HBV



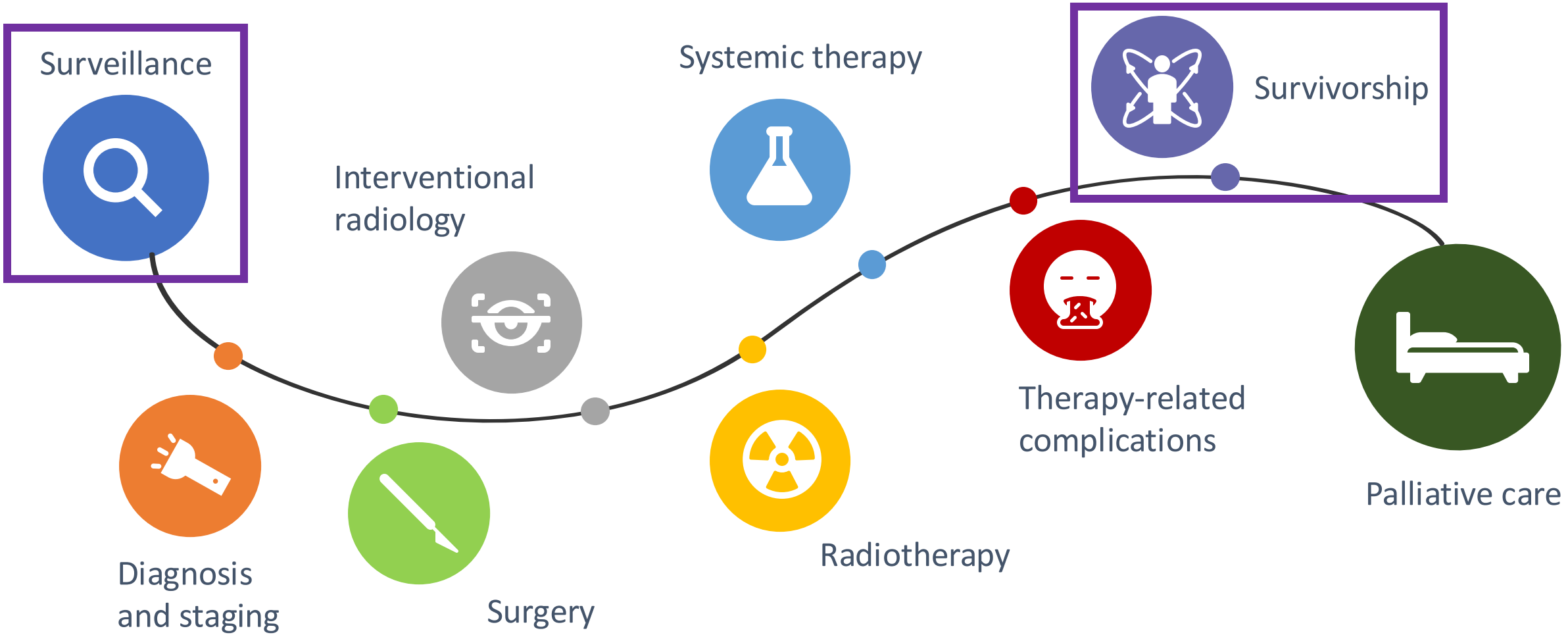
540 000 people
infected with HBV
22 000 people
infected with HCV

Around 50%
HBV-infected people were not aware of their HBV infection

1 552 people died of liver cancer in 2017



Unmet needs along a typical HCC patient journey



Overview

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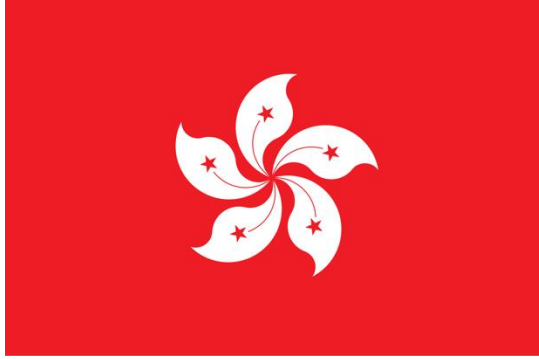
Hong Kong Association for the Study of Liver Diseases (HKASLD) HCC Surveillance Expert Meeting in 6/2023



Meeting agenda

Time	Session	Speaker
18:30–18:35 (5 mins)	Opening and Introduction of Meeting Objectives	Dr Loey Mak
18:35–18:50 (15 mins)	Current HCC Patient Journey in Hong Kong	Dr Rashid Lui
Part 1: The Value of New Biomarkers in HCC Surveillance		
18:50–19:10 (20 mins)	Clinical Data & Expert Opinions on PIVKA-II in HCC Surveillance	Professor Henry Chan
19:10–19:25 (15 mins)	The Value of PIVKA-II in HCC Surveillance: A Health Economic Perspective	Professor Yuen Man Fung
19:25–20:10 (45 mins)	Discussion: • Current Gaps in HCC Surveillance in Hong Kong • The Role of PIVKA-II as an Additional Biomarker in HCC Surveillance	All
20:10–20:20 (10 mins)	Break	
Part 2: The Application of New Biomarkers in Clinical Practice		
20:20–20:50 (30 mins)	Hospital Sharing: Local experience of using PIVKA-II in clinical practice	Professor Grace Wong, Dr James Fung, Dr Reggie Li
20:50–21:20 (30 mins)	Discussion: • Clinical Workflow for PIVKA-II Introduction in Hospital Settings • Appropriate Patient Selection of PIVKA-II Based Surveillance • Arrangement for Follow-up of Suspected Patients	All
21:20–21:30 (10 mins)	Summary and closing remarks	Dr Rashid Lui

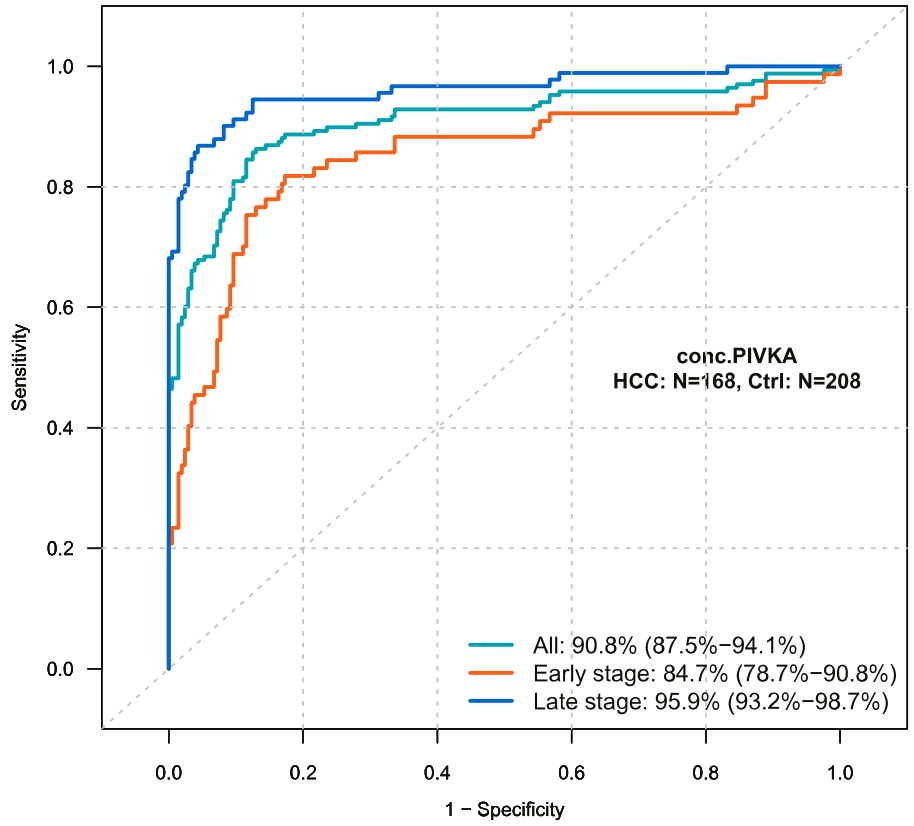
High sensitivity of PIVKA-II for the detection of HCC

	All HCC	Early Stage HCC[a)]	Late Stage HCC[b)]
Sensitivity[c)] (95% CI)	**86.9%** (80.8%, 91.6%)	**77.9%** (67%, 86.6%)	**94.5%** (87.6%, 98.2%)
Specificity (95% CI)	**83.7%** (77.9%, 88.4%)	**83.7%** (77.9%, 88.4%)	**83.7%** (77.9%, 88.4%)
ROC AUC[d)] (95% CI)	**90.8%** (87.5%–94.1%)	**84.7%** (78.7%–90.8%)	**95.5%** (93.2%–98.7%)

**95th percentile in the apparently healthy population)*

a) BCLC stages 0, A
b) BCLC stages B,C,D
c) Applies to sensitivity and specificity only
d) Area under the Curve

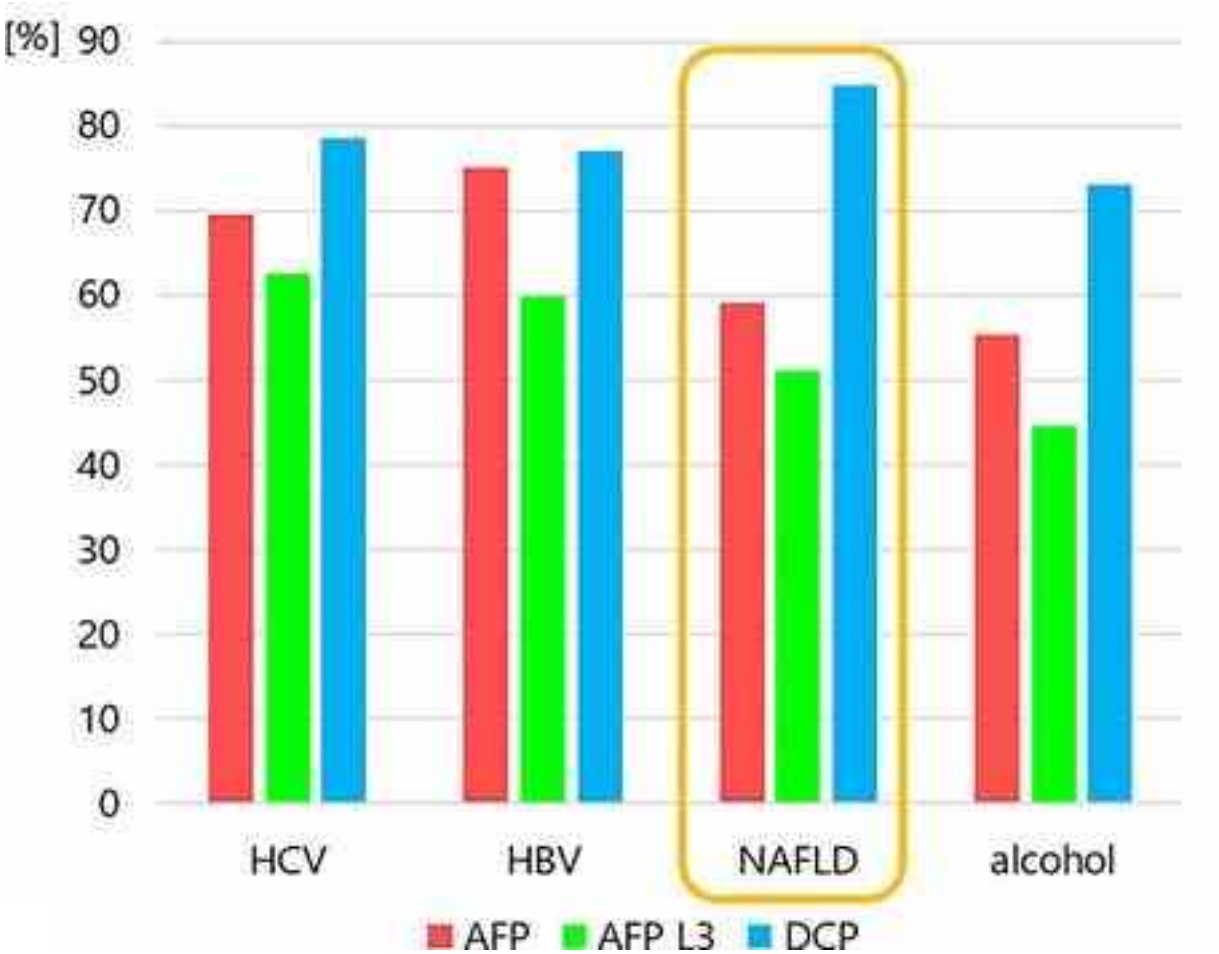
At a cut-off of 28.4 ng/mL shows high sensitivity combined with good specificity in detecting late-stage HCC



Chan HLY et al. JGH Open. 2022 May 7;6(5):292-300.

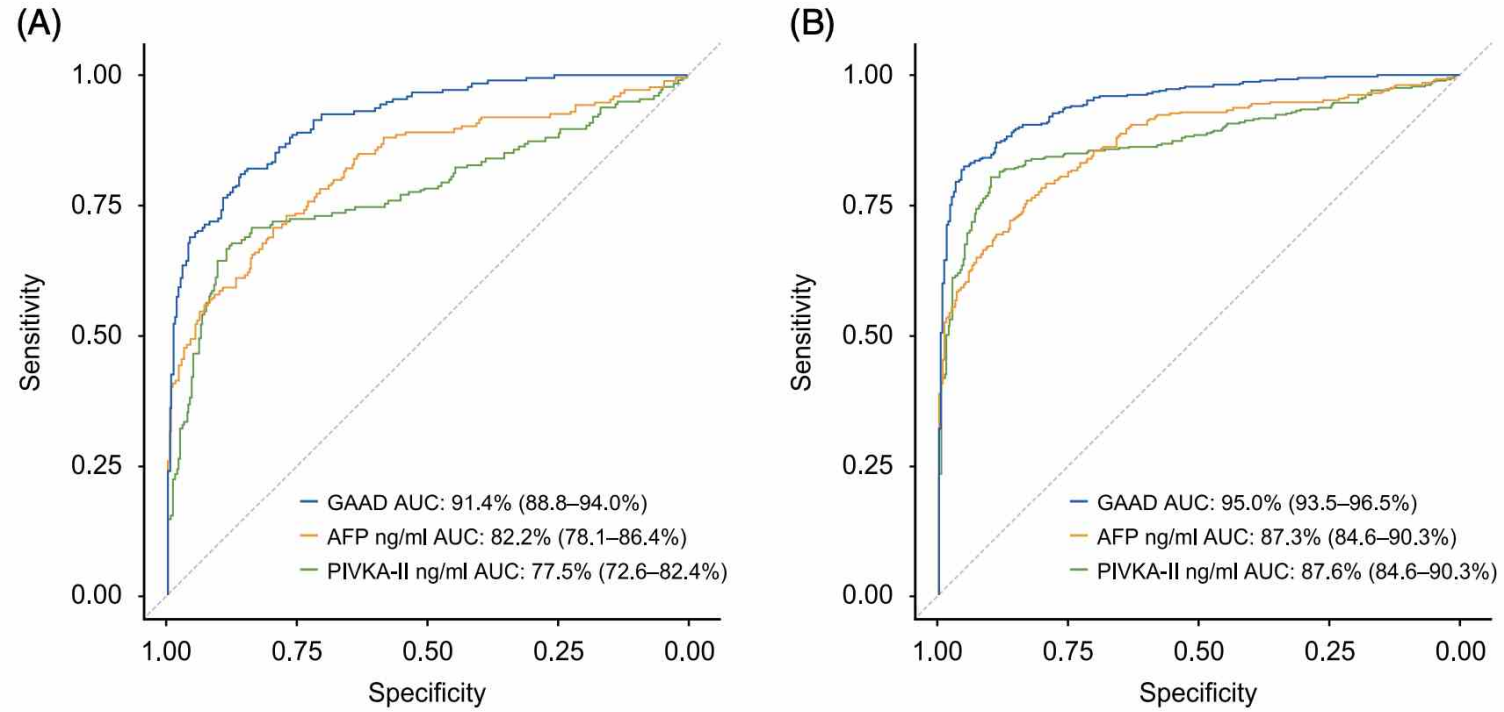
PIVKA-II may have a better diagnostic performance in MAFLD patients who are more likely to have AFP-negative HCC

Cut-off values:
AFP: 20 ng/dL
L3: 10%
DCP: 40 mAU/mL



Kudo M. Liver Cancer. 2024 Feb 20;13(2):113-118.

GAAD (gender, age, AFP, des-gamma carboxyprothrombin [PIVKA-II]) score



	Sensitivity, % (95% CI)		Specificity, % (95% CI)
	Early stage HCC (N=174)	All-stage HCC (N=366)	CLD controls (N=303)
Elecsys AFP assay (cut-off: 20 ng/mL)	41.4 (34.0–49.1)	53.8 (48.6–59.0)	98.0 (95.7–99.3)
Elecsys PIVKA-II assay (cut-off: 28.4 ng/mL)	60.9 (53.2–68.2)	78.4 (73.8–82.5)	90.4 (86.5–93.5)
GAAD score (cut-off: 2.57)	70.1 (62.7–76.8)	83.1 (78.8–86.8)	93.7 (90.4–96.2)

Piratvisuth T et al. Hepatol Commun. 2023 Nov 8;7(11):e0317.

Recommendations of the HKASLD HCC Surveillance Expert Meeting

1. Most experts recommended using **PIVKA-II in addition to AFP** because this combination has a better diagnostic performance compared with either biomarker alone. However, PIVKA-II cannot entirely replace AFP due to limited evidence and differing biological mechanisms.
2. Regardless of the biomarker(s) used, this approach **cannot replace the need for semi-annual liver USG** in HCC surveillance. This recommendation is particularly pertinent considering the long wait times for USG in the public sector. PIVKA-II may be useful in prioritising patient referrals to the private sector for imaging.
3. **PIVKA-II** is recommended for **special patient populations, such as those with cirrhosis, normal AFP levels, and non-viral aetiologies** of chronic liver disease (eg, MASLD and alcoholic liver disease), particularly when accompanied by cirrhosis.
4. The utility of the **GAAD score** has been demonstrated, but it is considered difficult to interpret for continuous monitoring because age increases each year.
5. Other potential roles for **PIVKA-II** include its use in **difficult or borderline cases**, where it may serve as a helpful adjunct to clarify the diagnosis, and for monitoring HCC recurrence in patients who have undergone HCC resection.

Lui RNS et al. Hong Kong Med J Hong Kong Med J 2024 Oct 16

Overview

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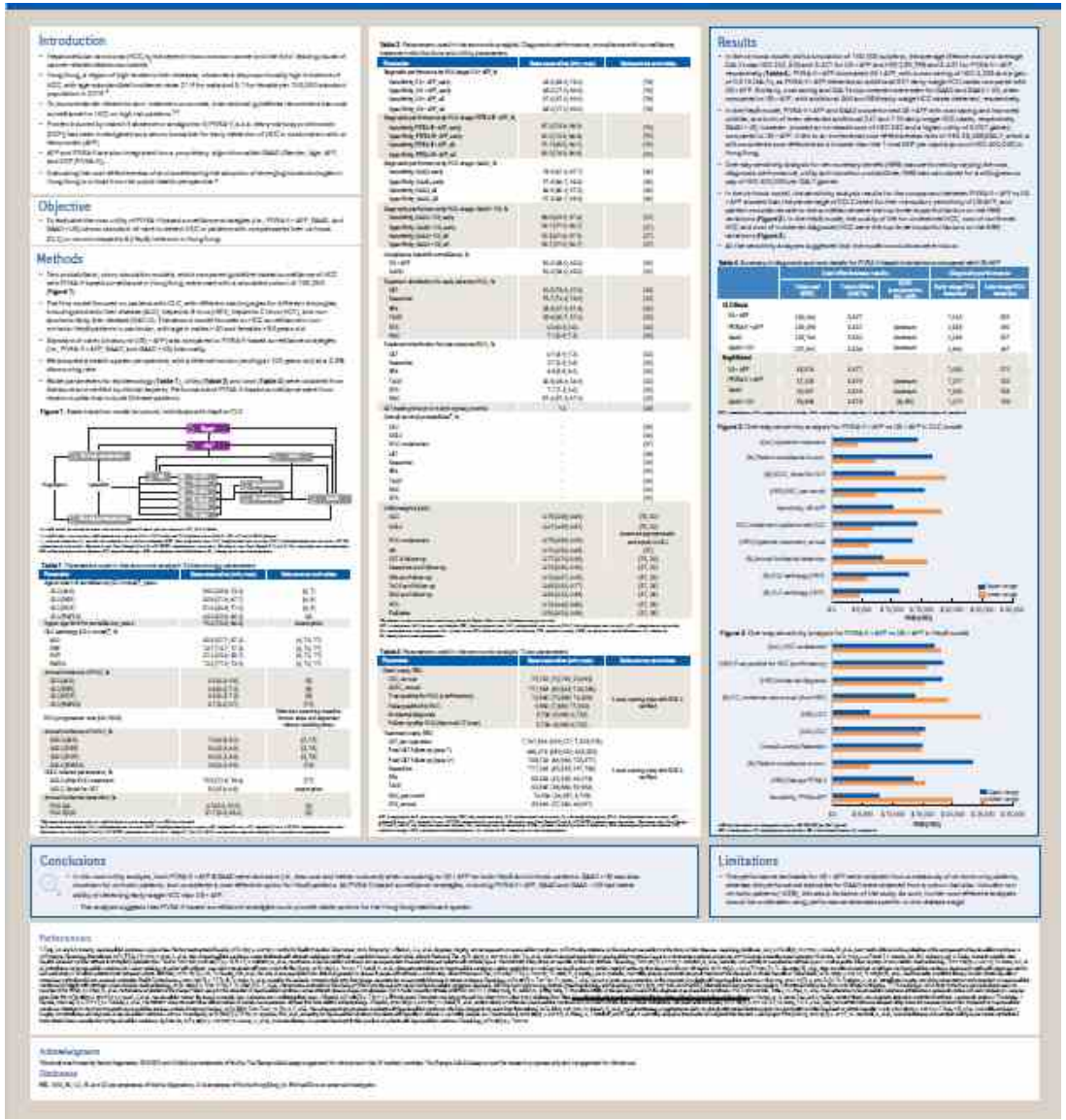
- **Health economics**
- HCC surveillance programmes in the Asia-Pacific

Hong Kong health economic (HECON) study on HCC surveillance



"Surveillance of hepatocellular cancer among hepatitis B and cirrhosis patients using Protein Induced by Vitamin K Absence-II (PIVKA-II): a cost-utility analysis for Hong Kong as an example of endemic regions"

Objective of the study:
Evaluate the cost utility of PIVKA-II based surveillance strategies (i.e., PIVKA II + AFP, GAAD, and GAAD + USG) vs standard of care (USG + AFP) to detect HCC

APASL 2023; Poster no. PPP-280

Model outcomes for liver cirrhosis

- With a simulation of 100,000 subjects, the average lifetime cost and average QALYs of Standard of Care (USG+AFP) was HKD 242,626 and 5.421 QALYs
- For PIVKA II + AFP, the average lifetime cost and average QALYs was HKD 239,298 and 5.437, with a **cost saving of HKD 3,328** and a **gain of 0.016 QALYs**, which is considered as a dominant strategy compared to standard of care
  - An **additional 521 cases with early-stage HCC** can be detected vs USG+AFP
- Similarly, cost saving and QALYs improvement were seen for GAAD and GAAD + USG, when compared to USG+AFP, with additional 360 and 558 early stage HCC cases detected, respectively.

	Cost-effectiveness results			Diagnostic performance	
	Total cost (HKD)	Total utilities (QALYs)	ICUR (compared to US + AFP)	Early-stage HCC detected	Late-stage HCC detected
CLC Model					
US + AFP	242,626	5.421	-	1,924	439
PIVKA-II + AFP	239,298	5.437	Dominant	2,445	290
GAAD	233,166	5.432	Dominant	2,284	321
GAAD + US	237,692	5.438	Dominant	2,482	281

APASL 2023; Poster no. PPP-280

Model outcomes for hepatitis B

- With a simulation of 100,000 subjects, the average lifetime cost and average QALYs of Standard of Care (USG+AFP) was HKD 45,576 and 5.471 QALYs
- For PIVKA II + AFP, the average lifetime cost and average QALYs was HKD 41,225 and 5.479, with a **cost saving of HKD 4,351** and a **gain of 0.008 QALYs**, which is considered as a dominant strategy compared to standard of care
  - An **additional 247 cases with early-stage HCC** can be detected vs USG+AFP
- Similarly, cost saving and QALYs improvement were seen for GAAD
- For GAAD+USG, when compared to USG+AFP, it showed an increased cost of HKD 282 and a higher utility of 0.007 gained, compared to USG+AFP. It led to an **incremental cost effectiveness ratio of HKD 35,455/QALY**, which is still considered **cost effective** as it is lower than the 1 time GDP per capita (around HKD 400,000) in Hong Kong.

	Cost-effectiveness results			Diagnostic performance	
	Total cost (HKD)	Total utilities (QALYs)	ICUR (compared to US + AFP)	Early-stage HCC detected	Late-stage HCC detected
HepB Model					
US + AFP	45,576	5.471	-	1,030	213
PIVKA-II + AFP	41,225	5.479	Dominant	1,277	143
GAAD	39,901	5.476	Dominant	1,200	154
GAAD + US	45,858	5.478	35,455	1,279	148

APASL 2023; Poster no. PPP-280

Conclusion of Hong Kong HECON study

- In the cost utility analysis, both **PIVKA II + AFP** & **GAAD** were dominant (i.e., less cost and better outcome) when comparing to USG + AFP for both Hepatitis B and cirrhotic patients

- GAAD + USG was also dominant for cirrhotic patients, and considered a cost effective option for Hepatitis B patients

- All PIVKA-II based surveillance strategies, including PIVKA II + AFP, GAAD and GAAD + USG had better ability of detecting early-stage HCC than USG + AFP

- This analysis suggests that **PIVKA-II based** surveillance strategies could provide viable options for the Hong Kong healthcare system

APASL 2023; Poster no. PPP-280

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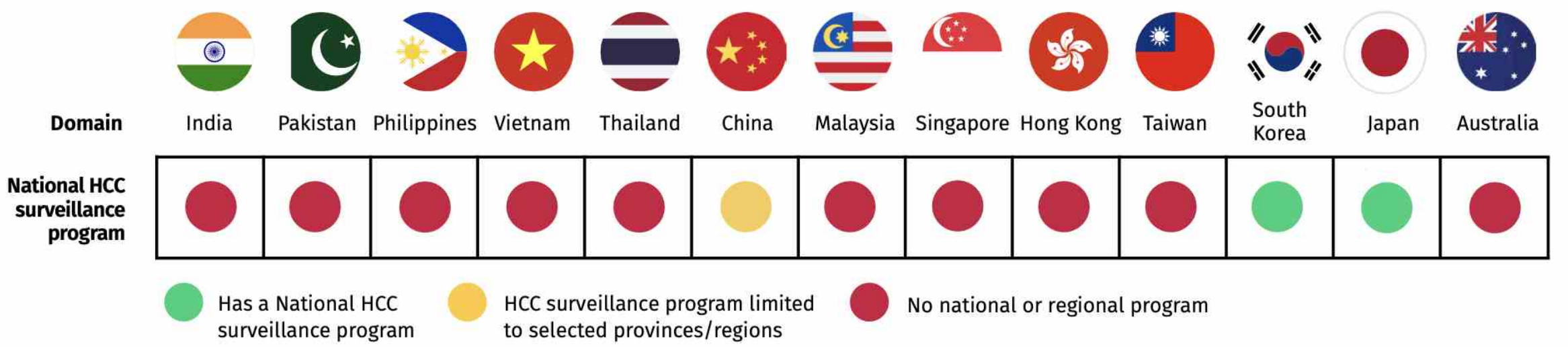
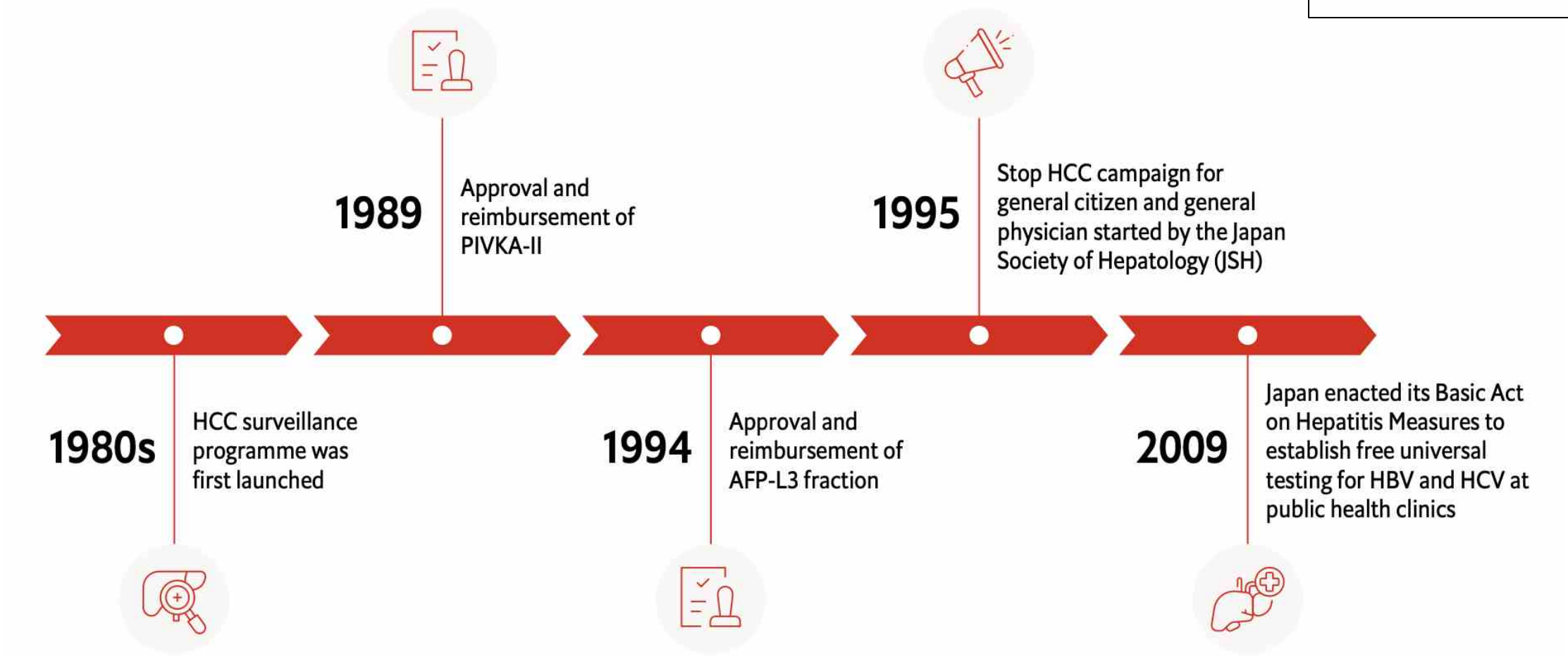
HCC surveillance programs in APAC



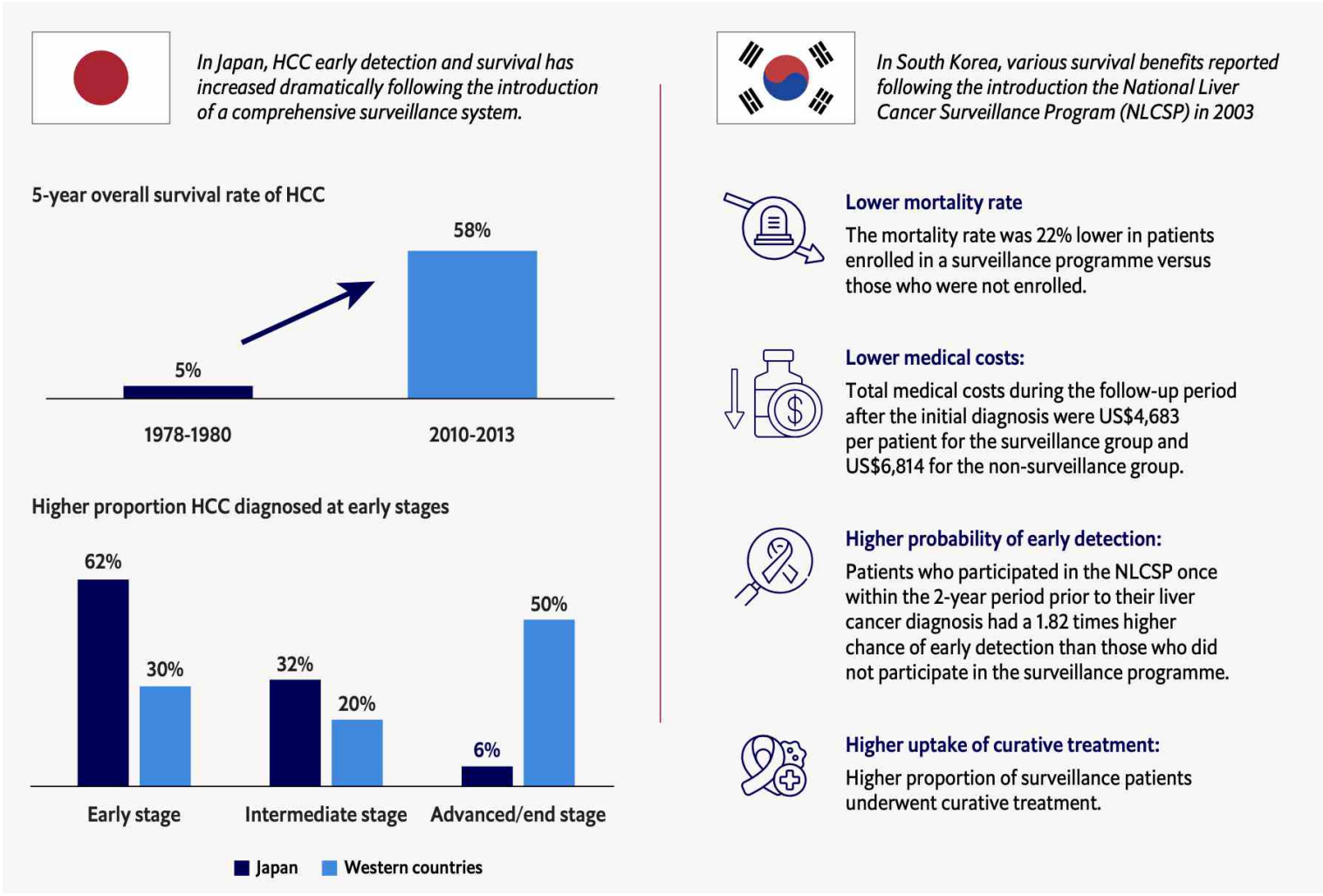
Eliminating Asia's silent emergency: hepatitis and hepatocellular carcinoma. APAC Liver Disease Alliance White paper 2023

Japan's world leading HCC surveillance programme



Building modern hepatocellular carcinoma surveillance programmes: taking steps to address a leading cause of liver cancer death in Asia - an Economist Impact report

Tangible benefits of national HCC surveillance programmes



Building modern hepatocellular carcinoma surveillance programmes: taking steps to address a leading cause of liver cancer death in Asia - an Economist Impact report

Improved survival likely due to earlier diagnosis of HCC

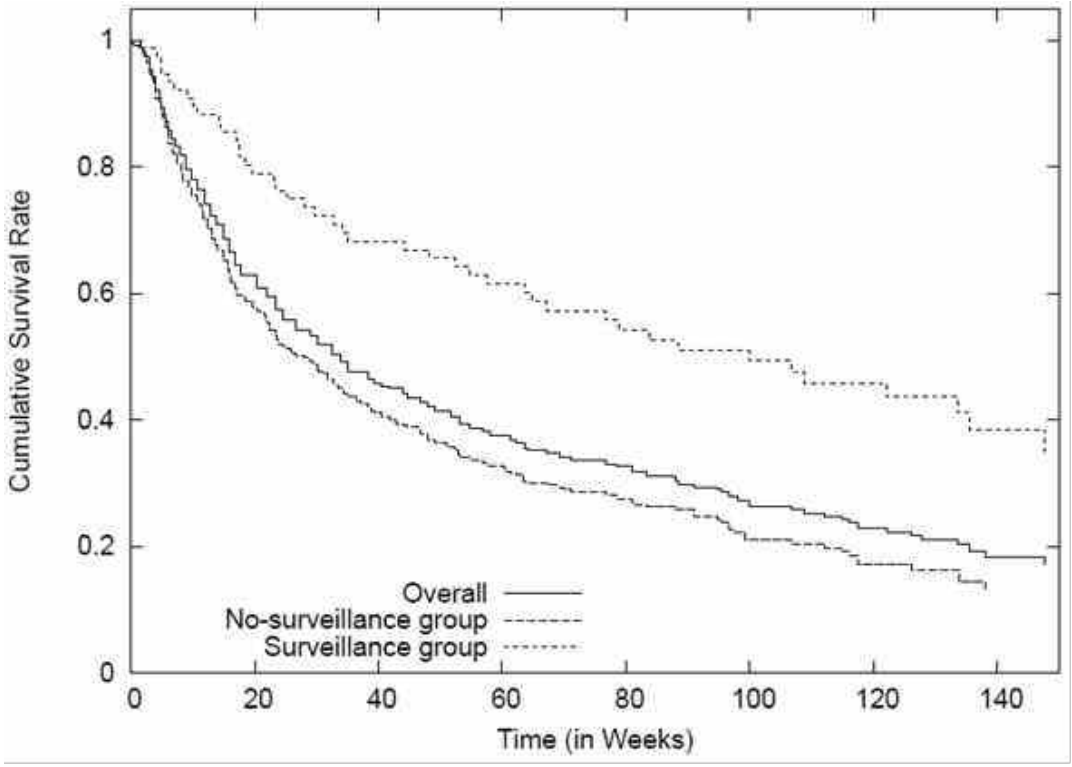
- **HCC surveillance: ultrasound scan + alpha-fetoprotein every 6 months**

Surveillance group:

Smaller HCC (4.2 cm *vs.* 7.7 cm; p<0.001)

Fewer HCC (2.6 *vs.* 3.8, p=0.03)

Longer survival (88 *vs.* 26 weeks; p<0.001)



37.6% of patients still died in 5 years

Bruix and Sherman. Hepatology 2012 Sep;56(3):793-6.
Wong GL et al. Liver Int 2008;28:79-87.

GAAD Digital Algorithm has been included in the latest edition of the Chinese National Health Commission’s guidelines

The GAAD Digital Algorithm has been Included in the National Health Commission's Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2024 Edition) Recommendations for the First Time

Recently, The Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2024 Edition) (hereinafter referred to as the “24th Edition Guidelines”), which was revised based 2022 Edition, was officially released by the National Health Commission (NHC).In this authoritative guideline document for liver cancer diagnosis and treatment, various liver cancer screening strategies are mentioned, including digital algorithms such as the GAAD model, which is based on gender, age, alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II). This is the first time that GAAD has been recommended for the early diagnosis of hepatocellular carcinoma (HCC). This inclusion provides new digital momentum for improving the standardized diagnosis and treatment of liver cancer in China, and demonstrates that the value of digital algorithms in the early diagnosis of liver cancer has been recognized.

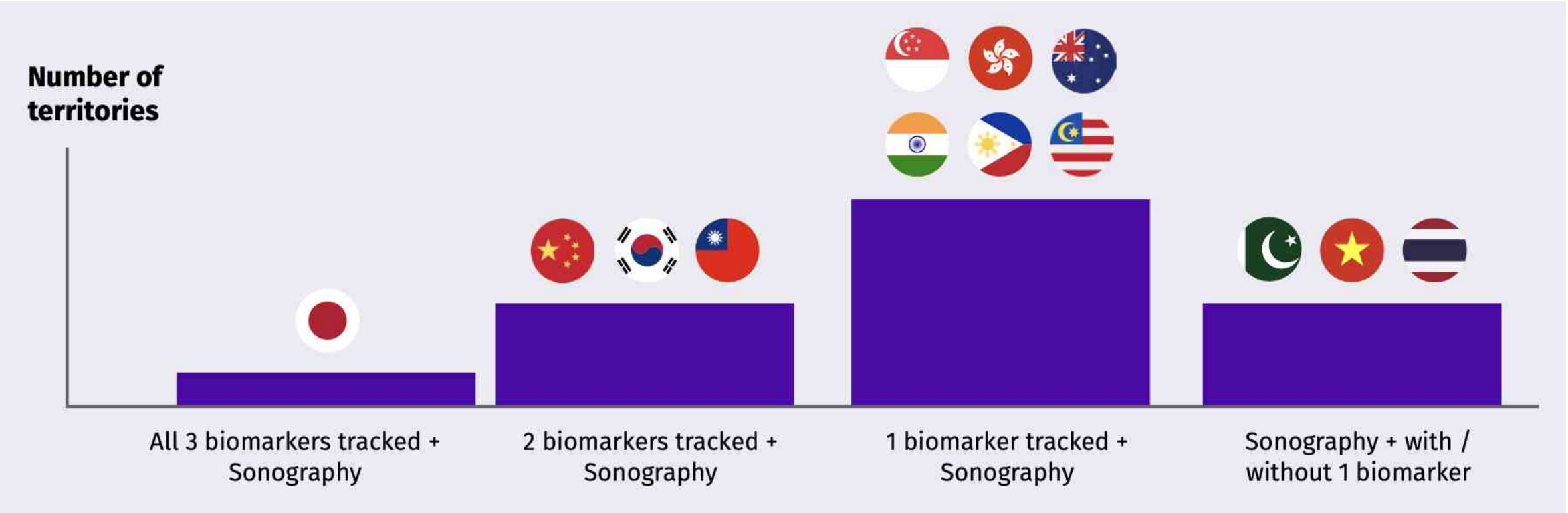
Asia-Pacific consensus on combining PIVKA-II and AFP in the surveillance and monitoring of HCC

Key statement	Agreement	Proportion
PIVKA-II in combination with AFP improves the detection of HCC, including small-sized tumours (≤3 cm), compared to either biomarker alone	Strongly agree	88.2%
PIVKA-II is valuable in the detection of HCC in AFP-negative HCC patients	Strongly agree	100%
Preoperative PIVKA-II measurement predicts the MVI risk, which may be useful in the assessment of tumour prognosis	Strongly agree	94.1%
PIVKA-II measurements, before and after curative treatment (resection and RFA), are useful for monitoring treatment outcomes and recurrence	Strongly agree	100%
PIVKA-II measurements, before and after intra-arterial treatment (TACE and TARE), are clinically useful to indicate response	Strongly agree	94.1%
Pre-liver transplant PIVKA-II levels are associated with the risk of post-operative HCC recurrence, potentially facilitating patient selection	Strongly agree	88.2%

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; MVI; microvascular invasion; PIVKA-II, protein induced by vitamin K absence II; RFA, radio-frequency ablation; TACE, transhepatic arterial chemoembolization; TARE, transhepatic arterial radioembolization.

Kim DY et al. Clin Mol Hepatol. 2023 Apr;29(2):277-292.

Overview of the number of biomarkers recommended by regional guidelines



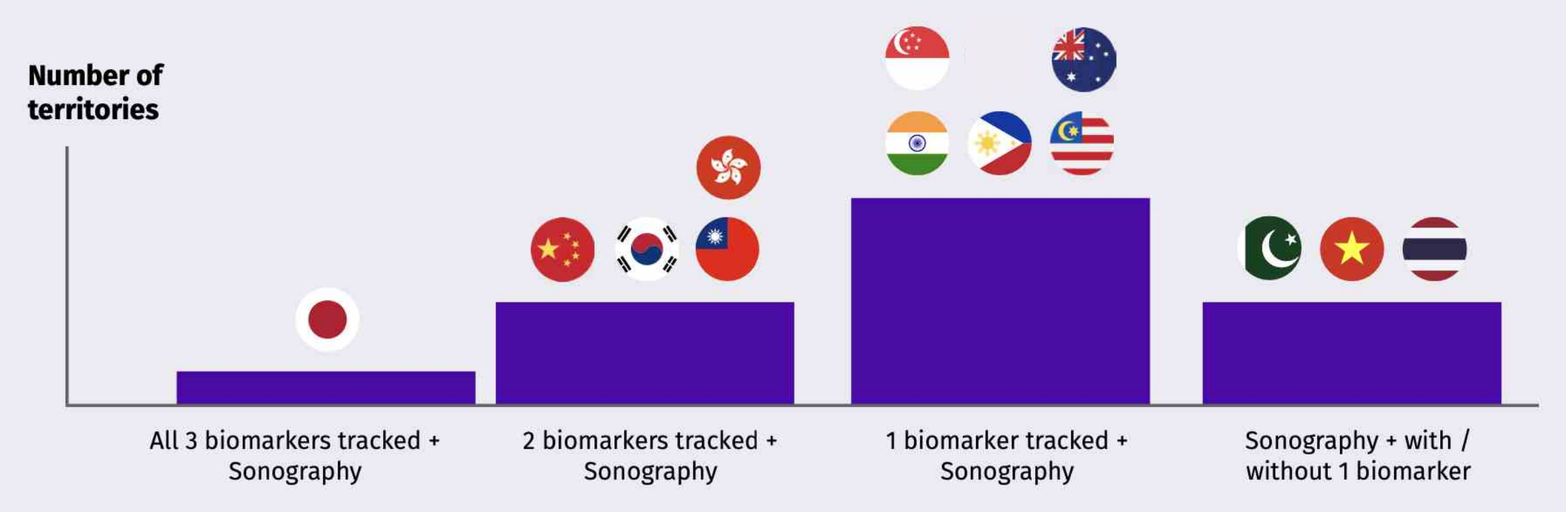
AFP
AFP-L3
PIVKA-II

AFP
PIVKA-II

AFP

Adapted from Eliminating Asia's silent emergency: hepatitis and hepatocellular carcinoma. APAC Liver Disease Alliance White paper 2023

Overview of the number of biomarkers recommended by regional guidelines



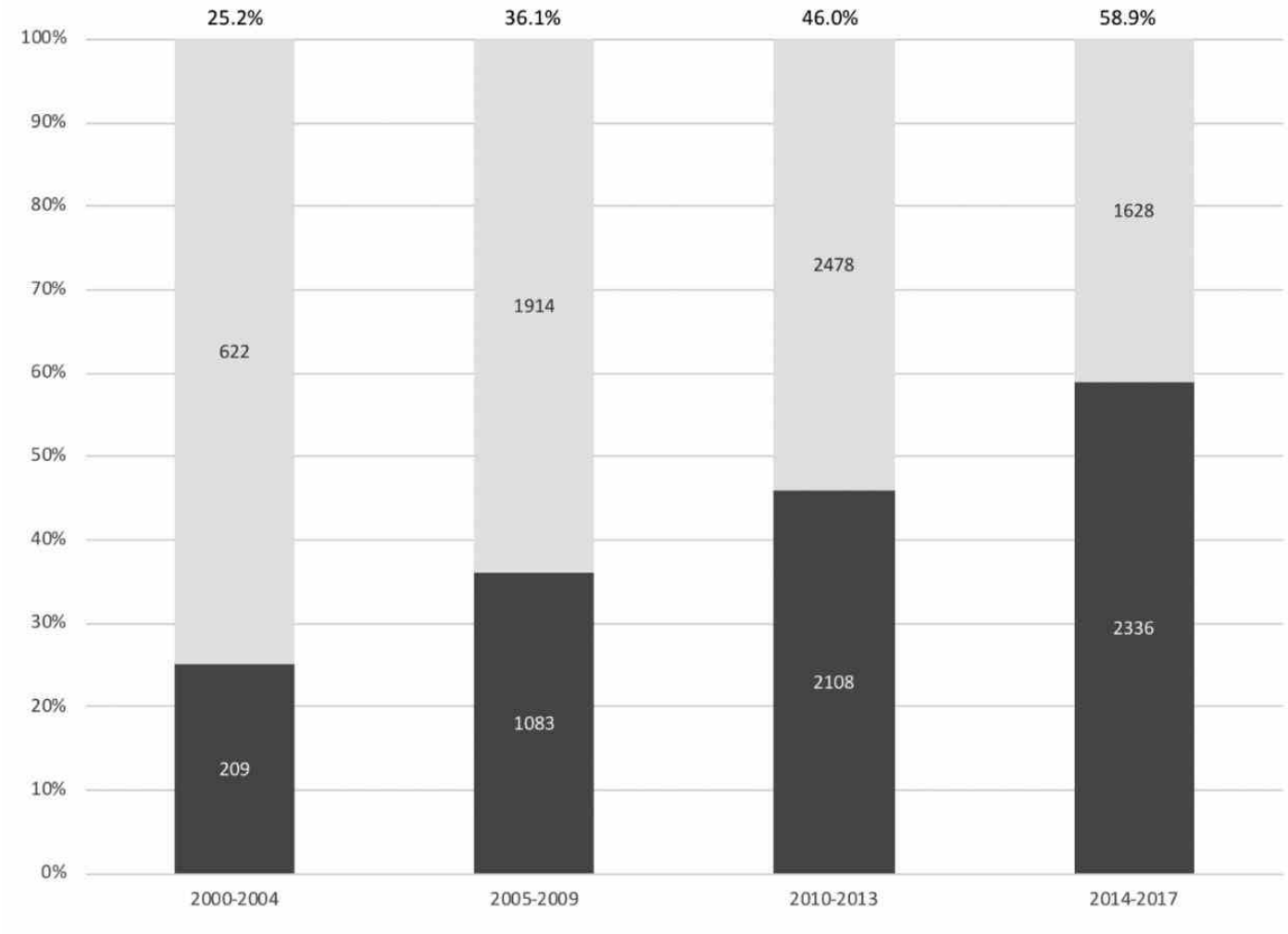
AFP
AFP-L3
PIVKA-II

AFP
PIVKA-II

AFP

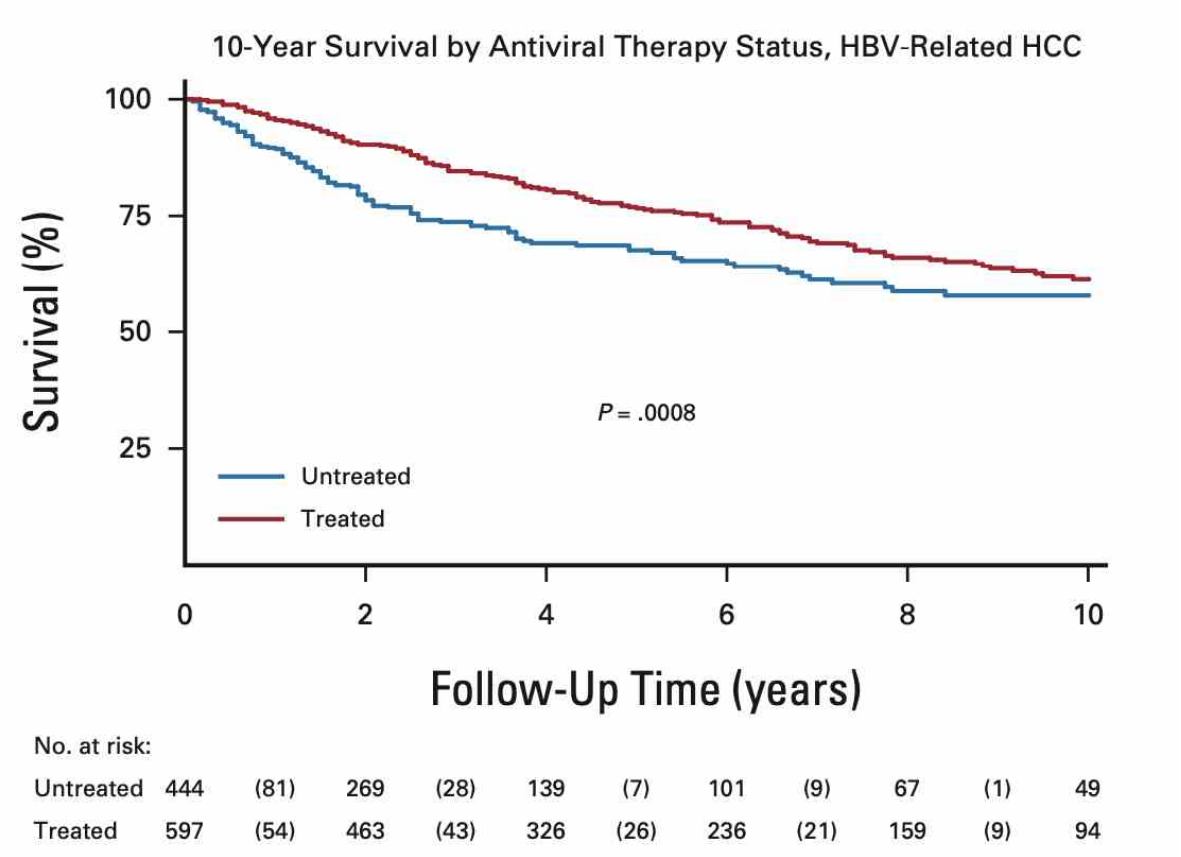
Adapted from Eliminating Asia's silent emergency: hepatitis and hepatocellular carcinoma. APAC Liver Disease Alliance White paper 2023

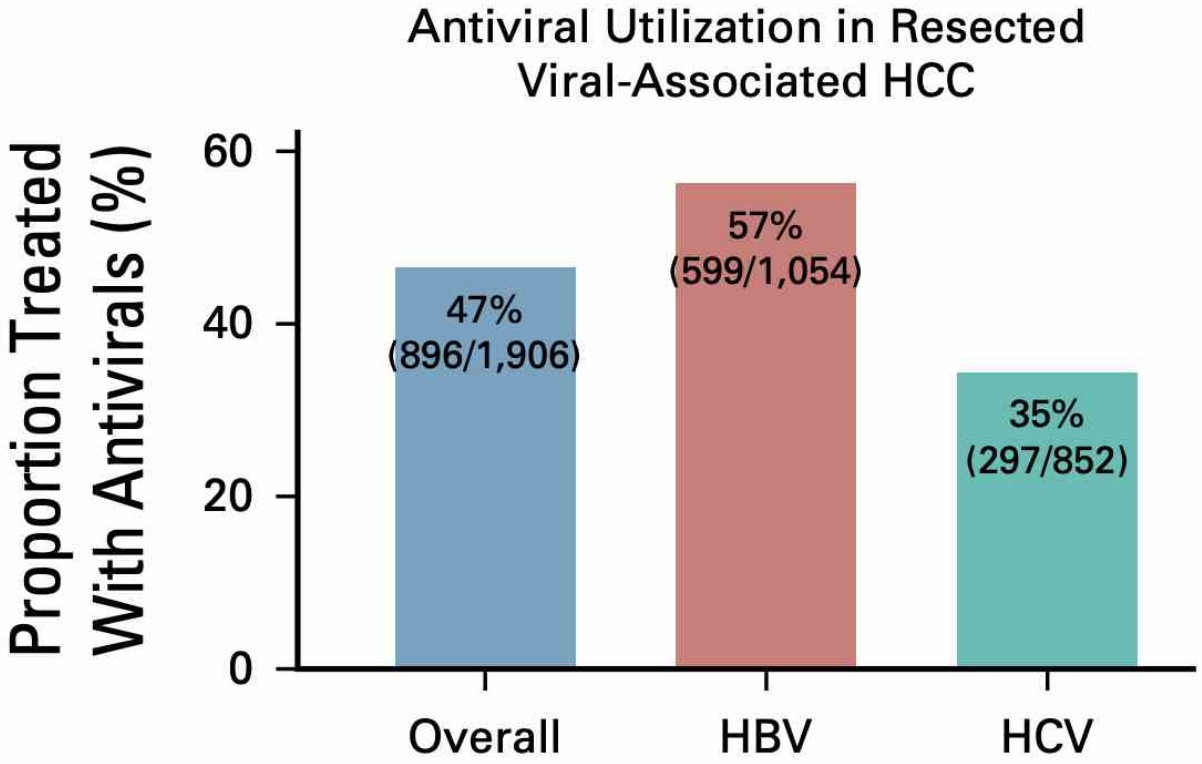
Hepatitis B treatment uptake <60% even for patients with liver fibrosis



Lai JC et al. J Gastroenterol Hepatol. 2021 Dec;36(12):3487-3499.

Antivirals improve survival but are underutilized in viral-associated HCC





Huang DQ et al. J Clin Oncol. 2024 Mar 1;42(7):790-799.

Take home messages

- Reducing the risk of HCC by **treating the underlying aetiology** of chronic liver disease is a top priority
- **Surveillance** and **early detection** for at-risk patients is the next best thing
- **Rise in MAFLD-related HCC** in Hong Kong, the Asia-Pacific and globally
- **Limitations** and **unmet needs** of **current screening modalities** and strategies
- **Adding PIVKA-II improves surveillance** strategies and is **cost effective** in our region

Questions are most welcome!

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