32nd Conference of the

Asian Pacific Association for the Study of the Liver (APASL 2023)

February 15 -19 2023
Taipei International Convention Center
Taipei, Taiwan

Conference Report

Overview

No	Sessions Covered
	Hepatitis C
1	Asia Hepatitis Strategy Summit
2	2023 APASL HCV Elimination Policy Forum
3	APASL Symposium 22-HCV: Natural History and Current Therapy (Including Special Populations)
4	Surveillance of HCC in patients with HCV after SVR: who and how
	Hepatitis B
5	APASL Symposium 3-HBV: Prevention, Natural History, Current Therapy and Indication
	Hepatocellular Carcinoma
6	HCC/CC: Epidemiology, Natural History, Diagnosis, and Staging
7	HCC/CC: Basic Science and Biomarkers
8	HCC/CC: Systemic Therapy Including Early Phase Data for Novel Treatments in HCC
9	Novel treatment strategy in intermediate - stage HCC
	Metabolic Associated Fatty Liver Disease
10	MAFLD: Diagnosis, Natural history, biomarkers and cancer

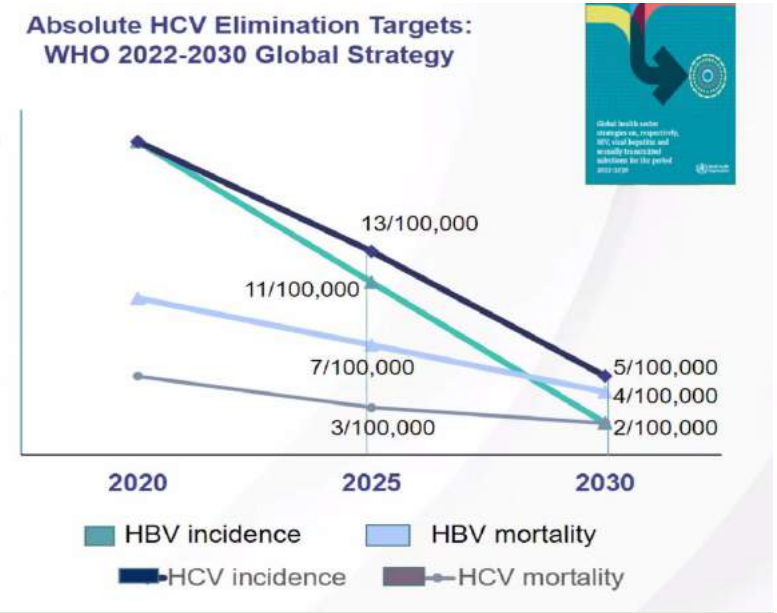
VIRAL HEPATITIS

1.Problem Statement

- HBV and HCV are large global health threats
- 3 million people are newly infected every year, with 1 million deaths.[1]

2. WHO Goals for Elimination of Viral Hepatitis

- Reduce the rate of new infections of Hep B+ C by 90% in 2030 compared to 2015.
- Reduce the number of deaths by 65% in 2030 compared to 2015.[2]



Key Takeaway:
Novel methods for diagnosis with effective control and treatment strategies are needed in order to achieve set goals for Hepatitis B and C elimination.

1. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/hepatitis-b
2. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies

Hepatitis C

This section contains the synopsis of the following sessions:

(I) Asia Hepatitis Strategy Summit

1. John Ward WHO'S Goal – GLOBAL PERSPECTIVE – WHO
2. Pei-Jer Chen Opening Remarks
3. Pei-Jer Chen- WHO Hepatitis Elimination Goal and Taiwan's Achievement
4. Jasmine Pwu Taipei Toward Hepatitis C Elimination by 2025 – Taiwan Policy and Strategies
5. Jia-Horng Kao HCV Progress to Eliminate & Best Practice: Taipei
6. Ming-Lung Yu Kaohsiung HCV Progress to Eliminate & Best Practice: Taiwan
7. Tetsuo Takehara Osaka HCV Progress to Eliminate & Best Practice: Japan
8. Jacob George Sydney HCV Progress to Eliminate & Best Practice: Australia
9. Panel Discussion: What's the Next Step Toward Elimination – Moderator Jia-Horng Kao (Taipei) Panelists Ming-Lung Yu (Kaohsiung) / Tetsuo Takehara (Osaka) / Jacob George (Sydney)

(II). 2023 APASL HCV Elimination Policy Forum

A. How Can a National Policy on HCV Elimination Help Achieve WHO Goals?

1. Jia-Horng Kao Taipei Opening Address- PATIENTS AS NORTH STAR
2. Philippa Easterbrook Geneva Guidelines on Simplified Service Delivery & The WHO Elimination Guidance and Criteria for validation of Elimination
3. John Ward Atlanta HCV Elimination Progress Among Asia Countries - Achievements & Opportunities
4. Naoya Kato Tokyo Section (II) Elimination Policy in General Population~ HEP C CAN'T WAIT
5. Christoph Sarrazin Wiesbaden HCV Elimination in Germany
6. Norifumi Kawada Osaka Countermeasures Against Viral Hepatitis in Japan

CONTD ON NEXT SLIDE

B. Road to HCV Elimination

1. Jae Young Jang Seoul Feasibility of National HCV Screening
2. Jin Gwack Osong National HCV Screening Strategies Moderator SiHyun Bae Seoul Panel Discussion
3. Panelists Jasmin Pwu (Taipei)/Junko Tanaka (Hiroshima)/Jeemin Park (Sejong)/ John Ward (Atlanta)

C. How Can a National Policy on HCV Elimination Help Achieve WHO Goals?

1. Rahul Kumar Singapore Elimination Policy in Special Population “NO PATIENT LEFT BEHIND” Prisoners Test & Treatment
2. Grace Lai-Hung Wong Hong Kong PWID Test & Treatment
3. What Does Success Look Like~ Call to Action- Ming-Lung Yu Kaohsiung Feedback & Closing Remarks

(III) APASL Symposium 22-HCV: Natural History and Current Therapy (Including Special Populations)

1. Fasiha Kanwal Houston Long-Term Outcomes of Chronic Hepatitis C Patients After Sustained Virological Response
2. Eiichi Ogawa Fukuoka: Predictors of Advanced Liver Disease of Chronic Hepatitis C Patients After Sustained Virological Response Following DAA
3. Chen-Hua Liu Taipei DAA Treatment in Hepatitis C Special Groups
4. Chia-Yen Dai Kaohsiung Unmet Needs in the Management

(IV) Surveillance of HCC in Patients With HCV After SVR: Who and How?

1. Ming-Lung Yu - Kaohsiung
2. Pierre Nahon - Paris

4 Symposiums = 27 lectures covered in 24 slides

WHO Perspective on Hep C Elimination

1.

- Goal - Hep C elimination by 2030
- Challenge - Identification and providing access to the “missing millions”- people living with Hep C, without access to healthcare

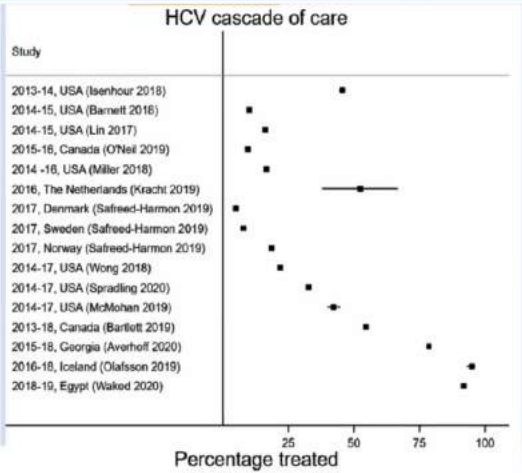
Challenges Faced in APAC Regions

- High proportion of patients developing HCC outside treatment criteria
- Need to involve non-specialists in care cascade
- In testing recommendations:

1. Reflex viral load testing is cost-effective and avoids additional blood draws
2. POC HCV RNA platforms can be optimized in lower health facilities, where they are already used for other disease testing.

Key Takeaway:
There is a need for shift in service delivery with a focus on DECENTRALIZATION and INTEGRATION of healthcare.
This moves care away from speciality clinics and into primary or community based facilities/ outreach services.

WHO HCV Updated Guidelines: Simple Guidelines Similar to Professional Societies

Simplified service delivery	HCV diagnosis	Use of DAA treatment of viremia patients ages =/> 3 years
- **Decentralization** (primary care, harm reduction sites, prisons and HIV/ART clinics, community-based organizations, outreach services)	- **Use of Point-of-care (POC) HCV RNA viral load to detect HCV infection** (as an alternative approach to lab-based diagnosis)	
- **Integration** (testing and treatment at the same services site)	- **Use of POC to assess treatment**	
- **Task sharing** (trained non-specialist doctors and nurses to expand access to dx, and treatment)	- **Reflex HCV RNA viral load testing**	

WHO Updated recommendations on simplified service delivery and diagnostics for hepatitis C infection. https://www.who.int/publications/i/item/9789240052697

J Viral Hepat. 2021;28:1340–1354.

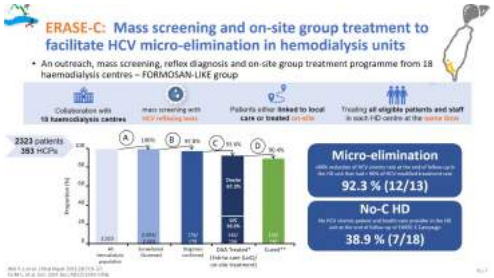
Key Takeaway: There has been a concerted effort to simplify and consolidate the WHO treatment guidelines for Hep C, so that they are similar to those proposed by different professional societies.

Strategies employed for Hep C Control - Country Examples

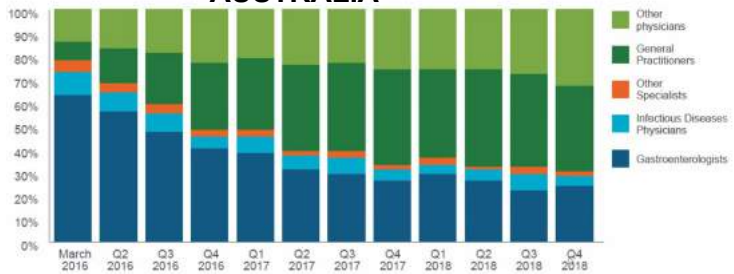
TAIWAN

Taiwan

1. Active Mass Screening Programs resulted in an anti-HCV reporting rate of 90.8%
2. Micro Elimination in Target Populations
   - Identification of target groups based on risk of transmission
   - Drawing heat maps to get a visual idea of disease risk
3. Real Time Road map (e-Roadmap) visualized progress made and next steps needed



AUSTRALIA



Increasing involvement of non-specialists in Hep C treatment

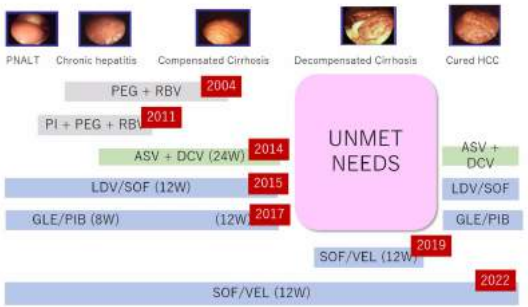
Australia

1. Unrestricted DAA access
2. Decentralization of prescriptions
3. Involvement of PCPs and non-specialists in prescribing DA

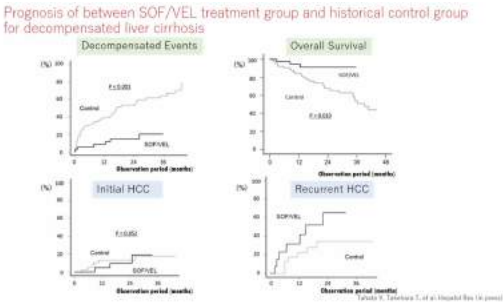
JAPAN

Japan

- Many elderly patients suffer from advanced liver disease
- Strategy focused on reducing the incidence of liver disease, along with Hep C Elimination
- Introduction of SOF/VEL (12 week regimen) in 2022, shows good prognosis for patients with decompensated liver cirrhosis



Action Taken



Positive Results Seen

Policy Led initiatives in Different Countries Toward Hep C Elimination

Germany

- Introduced “Check up 35” which offers general screening for people above the age of 35
- Includes HbsAg, HCV Ab, reflex testing, HBV- DNA and HCV-RNA.
- Screening performed by GPs to reduce burden on specialists

Japan

- National Hepatitis Program has decreased the incidence of Hep C in the region
- Introduced an Elimination Network in the Care Cascade, including - Testing + Linkage to Care + Treatment Uptake
- Electronic medical records alert systems in hospitals identifies infected patients and promotes intra-hospital referral to hepatologists

Korea

- Implemented National HCV Screening for people between the ages of 45-65 years
- Better outcomes with improved cost-effectiveness

Taiwan

- Implemented “No Patient Left Behind” initiative to test and treat PWID in at- risk populations - prisons
- CHIPS - C 2019 initiative - integrates HCV care into existing health programs for greater outreach

Hong Kong

- Initiated HCV screening for patients at methadone clinics with fast track referrals of cases to specialists
- Used finger-prick POC testing for anti-HCV and HCV RNA
- All DAAs are provided free from the government since October 2020.

Singapore

Launched the END-C initiative

- ETT platform for PWID- Educate, Test and Treat patients in prisons or halfway houses
- Integrated with Detoxification programs at Institute of Mental Health
- Collaborations with the National Centre for Infectious Diseases to identify co-infections in at-risk groups.

PANEL DISCUSSION : What are the next steps towards elimination of Hep C?

1. Acquire real time data on the progress of programs, allowing re-adjustment and calibration of initiatives.
2. Leverage AI to help with data collection and analysis in real-time dashboards for transparency and visualization of goals.
3. Micro- elimination is an effective method to target high risk populations, along with wide scale national programs.
4. Use call- back programs to actively follow up with patients.
5. Commitment towards more testing and screening initiatives to identify asymptomatic carriers
6. Decentralize prescription powers to allied healthcare professionals (nursing practitioners) or PCPs to start treatments faster
7. Simplify treatment protocols to encourage primary care physicians to actively treat cases in their communities.

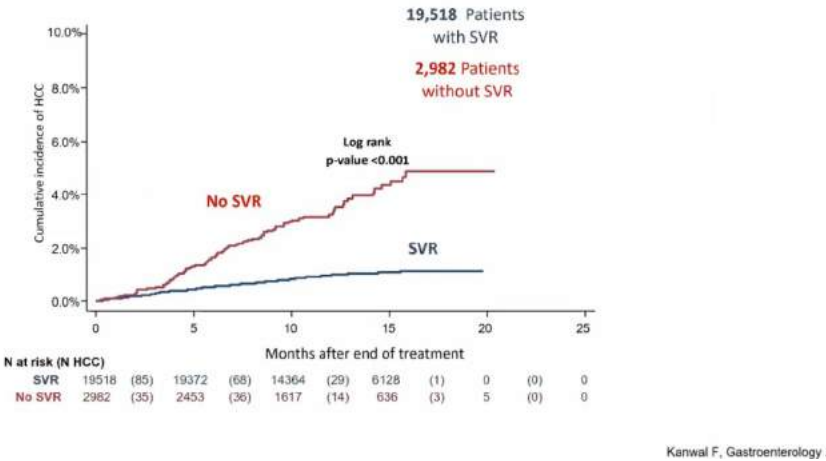
Long-Term Outcomes of Chronic Hep C Patients After Sustained Virological Response

Clinically important outcomes in patients with HCV:

1. Progression of liver disease - fibrosis, cirrhosis, decompensation
2. Hepatocellular carcinoma (HCC)
3. Mortality
4. Non-liver outcomes

The risk of HCC in patients with SVR

- 5X in cirrhosis
- 2X in alcoholic liver disease
- old age
- Portal hypertension
- Advanced fibrosis
- Poor hepatic functional reserve (Low ALBI score)
- ASH/NASH
- History of HCC



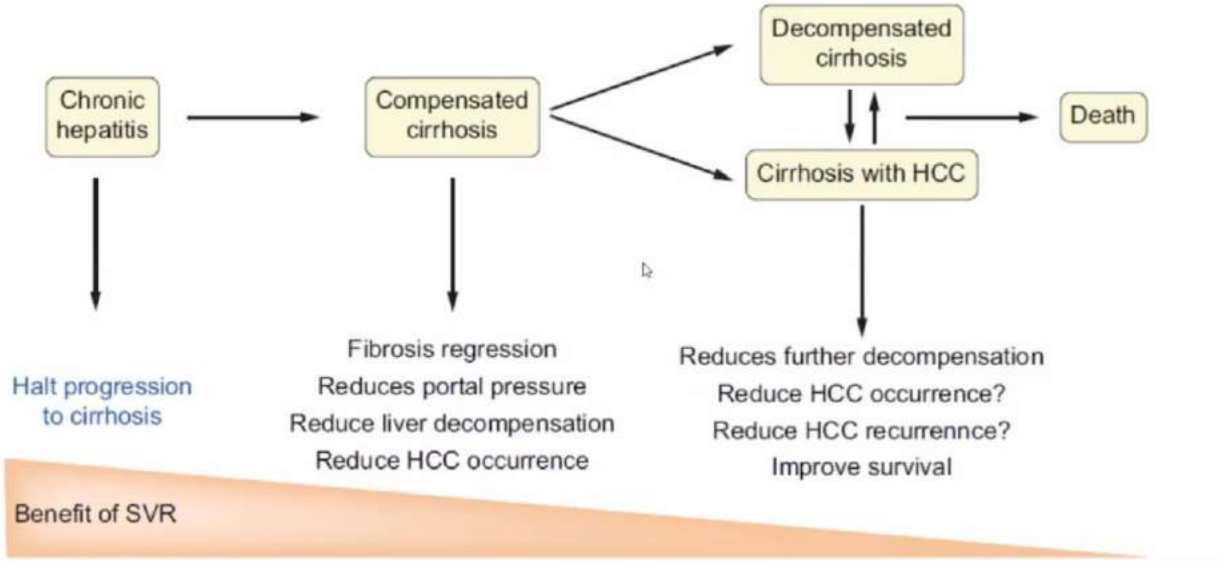
Kanwal F, Gastroenterology

Patients with advanced liver fibrosis or cirrhosis at the time of DAA treatment remain at risk for HCC after DAA-induced SVR. These patients should stay under HCC surveillance.

Cumulative incidence of hepatocellular cancer (HCC) among 22,500 patients treated with DAA agents. SVR, sustained virological response

Key takeaway: Sustained virologic response (SVR) after direct acting antiviral agents (DAAs) holds promise for reducing hepatocellular cancer (HCC). There are now several studies showing the survival benefit of SVR in HCV patients, including those with compensated cirrhosis.

Hepatic benefit of SVR according to stage of liver disease



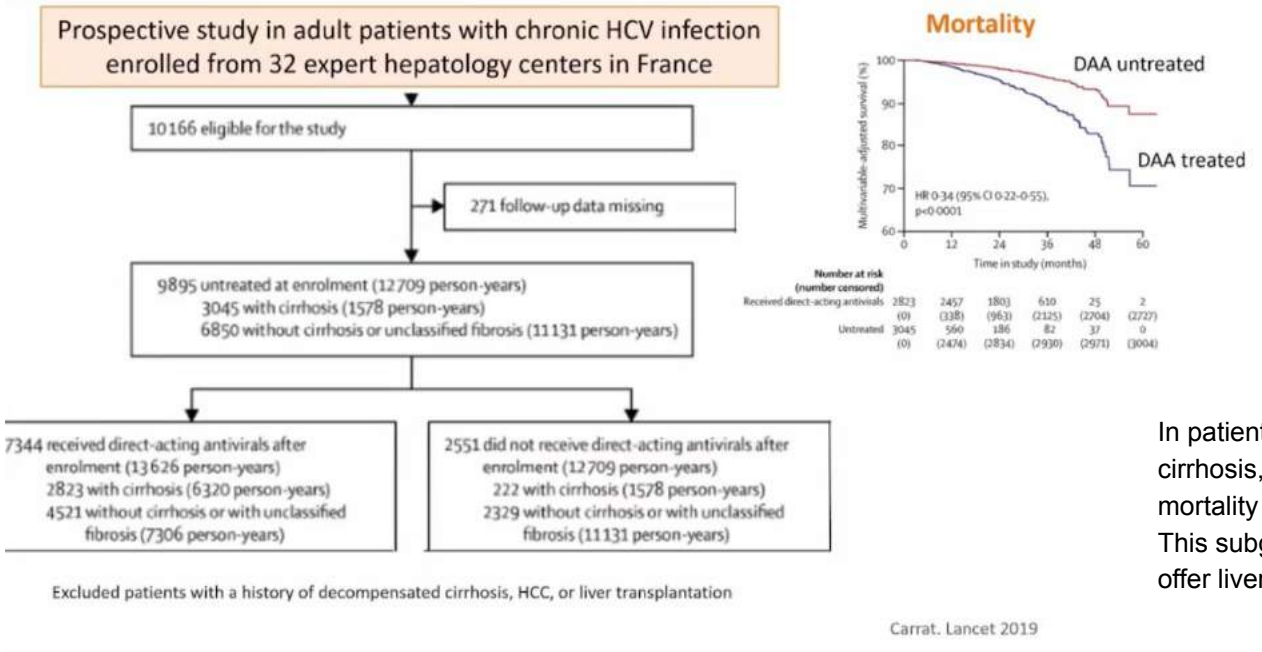
DAA -induced HCV clearance leads to improved outcomes at all stages of liver disease.

However the maximum measurable benefit is obtained by treating patients before they reach the stage of compensated advanced chronic liver disease (cACLD).

Key Takeaway: Ideally, all patients with chronic hepatitis C should be treated before they develop advanced fibrosis or cirrhosis.

Calvaruso, Vincenza, and Antonio Craxì. "Hepatic benefits of HCV cure." *Journal of hepatology* vol. 73,6 (2020): 1548-1556. doi:10.1016/j.jhep.2020.08.006

Association of DAA treatment with Mortality

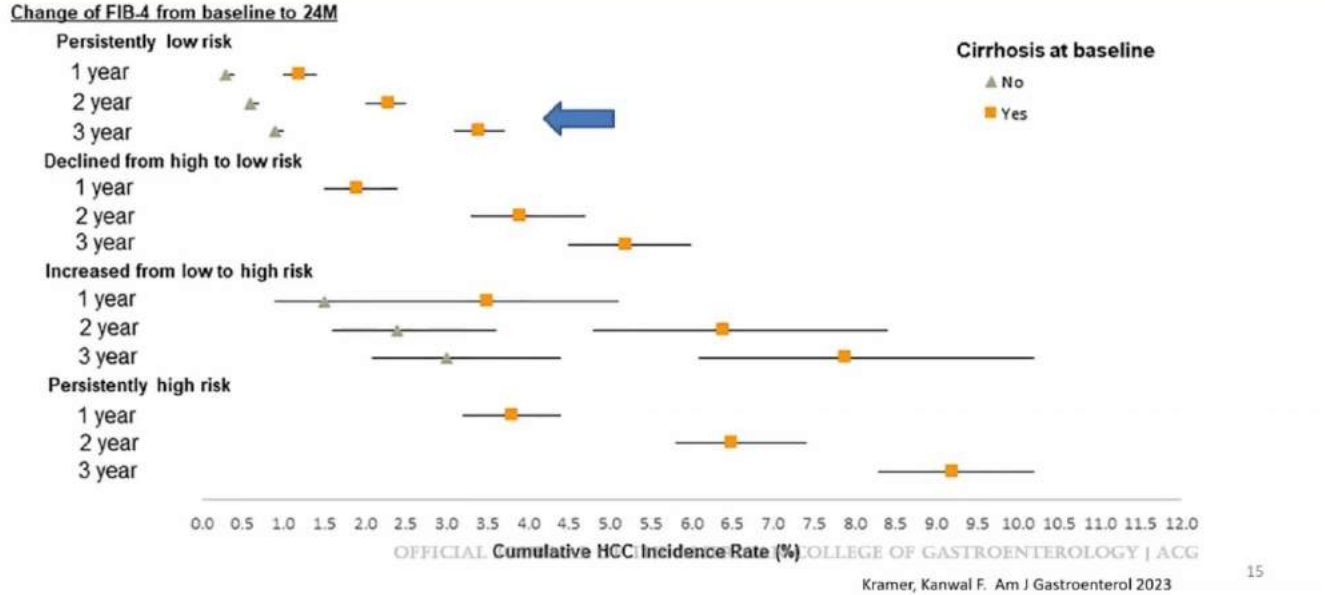


In patients with advanced or decompensated cirrhosis, the risk of further decompensation and mortality may remain high regardless of SVR. This subgroup should be managed in centers that offer liver transplantation.

Key Takeaway: Treatment with direct-acting antivirals is associated with reduced risk for mortality and hepatocellular carcinoma and should be considered in all patients with chronic HCV infection.

Carrat, Fabrice et al. “Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study.” *Lancet (London, England)* vol. 393,10179 (2019): 1453-1464. doi:10.1016/S0140-6736(18)32111-1

Risk Stratification for HCC in patients with SVR using FIB score



The risk of HCC was the highest in patients who had persistently high FIB-4/APRI and both with and without cirrhosis. HCC risk fell in patients with cirrhosis who experienced a decrease of FIB-4/APRI scores yet remained higher than the accepted threshold for HCC surveillance.

Key Takeaway: Monitoring changes in markers like FIB-4 could define risk stratification for HCC in patients with SVR.

https://doi.org/10.1002/hep.30823

FAST score as a predictive factor for HCC

FAST score

FibroScan-AST(FAST) score

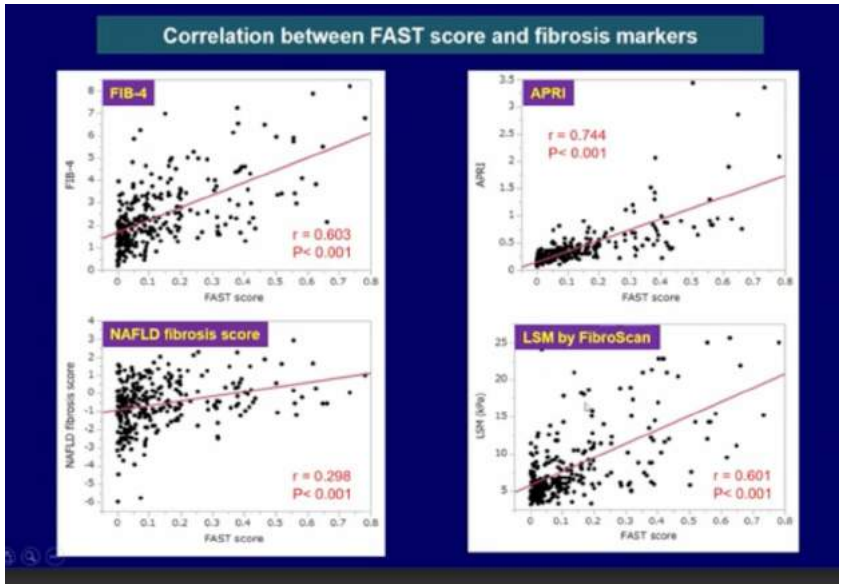
$$FAST = \frac{e^{-1.65 + 1.07 \times \ln(LS) + 2.66*10^{-4} \times CAP^{3} - 63.3 \times AST^{-1}}}{1 + e^{-1.65 + 1.07 \times \ln(LS) + 2.66*10^{-4} \times CAP^{3} - 63.3 \times AST^{-1}}}$$

① FibroScan score
② CAP score
③ AST level

FibroScan®

Effective for the diagnosis of high risk NASH (cut off : 0.35)

Newsome PN et al. Lancet Gastroenterol Hepatol 2020; 5: 362–73



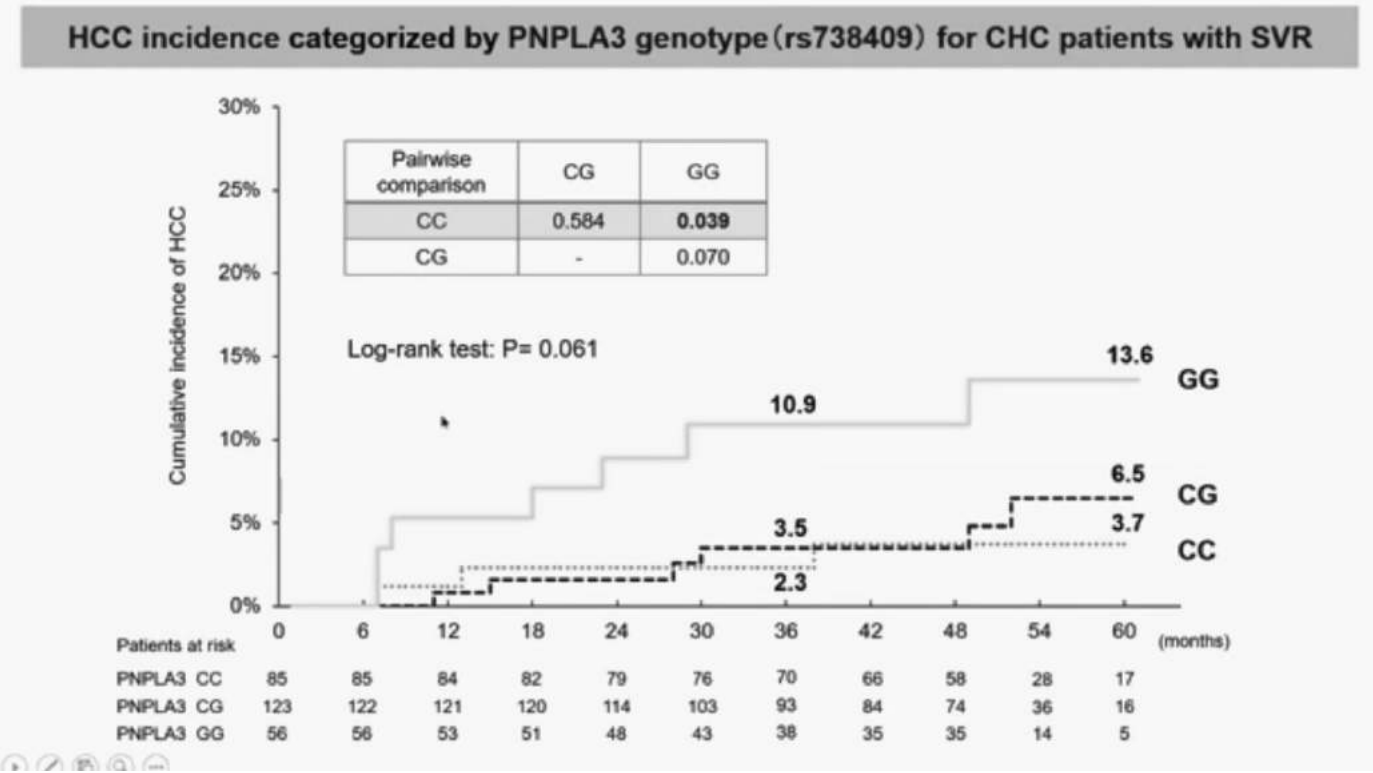
Incidence rate of HCC stratified by the FibroScan value (LSM)

	Patients, n	HCC, n	PY of follow-up	Incidence rate of HCC per 100 person-years (95%CI)	Adjusted HR* (95%CI)	P value
LSM < 10 kPa						
FAST score						
< 0.35	182	1	720.5	0.14 (0-0.60)	1	0.045
≥ 0.35	6	2	21.1	9.48 (0-23.8)	27.4 (1.08-700)	
LSM ≥ 10 kPa						
FAST score						
< 0.35	64	5	246.4	2.03 (0-4.06)	1	0.018
≥ 0.35	28	6	102.6	5.85 (0-10.8)	4.41 (1.30-15.0)	

* Adjusted for age, sex, FIB-4 index, and serum albumin, ALT, AFP at 12 weeks after the end of DAAs

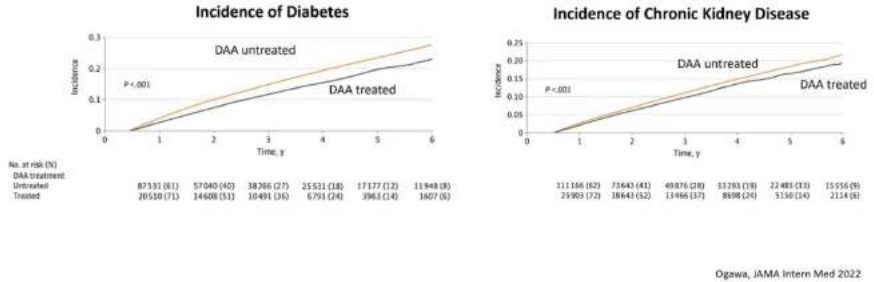
Key Takeaway: FAST scan is a more useful predictive factor for the development of HCC than only LSM Fibroscan value.

Genetic marker for HCC incidence in patients with SVR

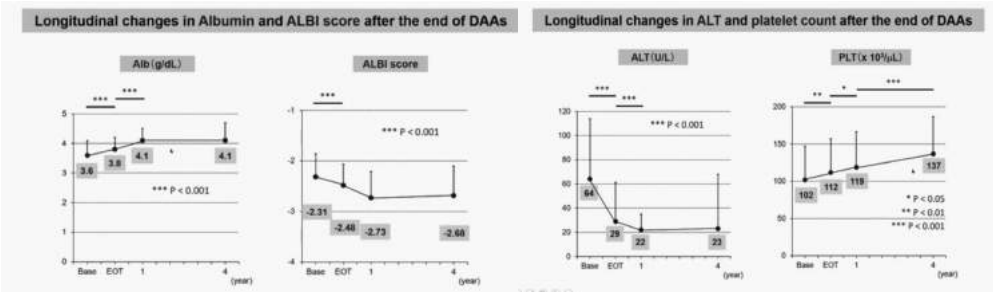


Key Takeaway: Patients with with a GG - PNPLA3 genotype have a higher risk of HCC than those with a CG genotype.

Non-liver outcomes of patients treated with DAA



Ogawa, JAMA Intern Med 2022



Key Takeaway:

1. The long-term benefits of SVR extend beyond the liver to include outcomes like decreased incidence of diabetes and chronic kidney disease.
   Stabilization of albumin, ALBI scores, ALT and platelet counts

2. HCV clearance eliminates the risk of virus transmission with great public health benefits

DAA Treatment in Special Groups with Hep C Infections

Group	HCV + organ donors for HCV-recipients	Severe renal impairment	Acute Hepatitis C	HBV co-infection	PWID patients	Children and adolescents	Pregnancy
Challenge	Universal transmission following transplantation Potential fibrosis due to immunosuppression. Graft survival impaired Poor tolerance to PR. Potential DDI to immunosuppressants	Higher risk of mortality Recurrent HCV infection even after renal transplant. Polypharmacy leads to potential DDI .Impact of PK on some drugs due to poor renal clearance.	Difficulty in achieving a confirmed diagnosis until seroconversion Controversies about waiting for spontaneous viral clearance and the risk of viral transmission	Faster progression of fibrosis and HCC Potential HBV reactivation following DAA	Poor patient compliance High risk of reinfection	Concerns for altered PK profiles	Concern for altered PK profiles and safety for babies
Solution	Pre-emptive administration of glecaprevir-pibrentasvir results in expedited organ transplantation, rapid HCV suppression, prevention of chronic HCV infection, and excellent early allograft function in patients receiving HCV-infected donor hearts	**EXPEDITION 4 STUDY:** Glecaprevir/pibrentasvir for HCV GT 1-6 patients with renal impairment gave a sustained virologic response rate of 98%	**HepNet acute HCV-V study:** 8-week treatment with SOF/VEL was well tolerated and highly effective in acute HCV mono-infection. **REACT Study** 6-week sofosbuvir-velpatasvi appeared to be less effective than a standard 12-week course	12 weeks of entecavir is suggested to be co-administered with DAA for HCV/HBV dually infected patients to prevent HBV virologic reactivation (HBVr) and clinical reactivation (CR) during DAA treatment	Well tolerated treatment regimes indicate that physicians should not discourage DAA for PWID Harm reduction should be done for patients with high risk behaviors	SOF/VEL for 12 weeks resulted in an SVR12 rate of 92% in patients between 3 and 17 years Adolescent patients with chronic HCV infection treated with glecaprevir and pibrentasvir achieved a comparable exposure to adults, a 100% SVR12 rate, and a safety profile consistent with that in adults	Ledipasvir-sofosbuvir was safe among pregnant and non-pregnant women
Ref	https://pubmed.ncbi.nlm.nih.gov/31353243/	https://pubmed.ncbi.nlm.nih.gov/31353243/	https://pubmed.ncbi.nlm.nih.gov/34023350/ https://pubmed.ncbi.nlm.nih.gov/36852107/	https://pubmed.ncbi.nlm.nih.gov/34864158/		https://www.natap.org/2020/AASLD/AASLD_26.htm https://pubmed.ncbi.nlm.nih.gov/31254392/	https://pubmed.ncbi.nlm.nih.gov/32939459/

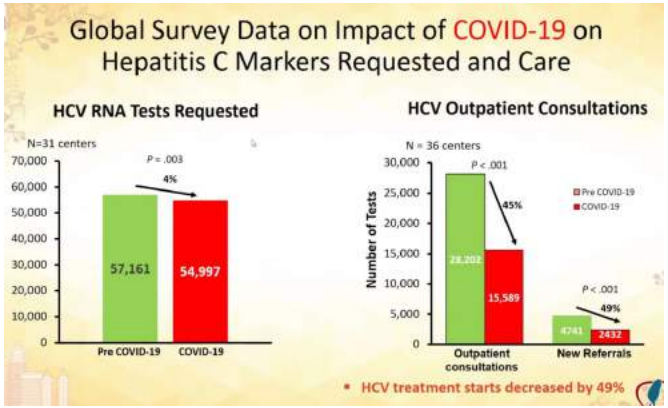
Key takeaway: Health outcomes can be improved following SVR by DAAs with overall efficacy and safety benefitting special groups.

Unmet Needs in the Management of Chronic Hepatitis C

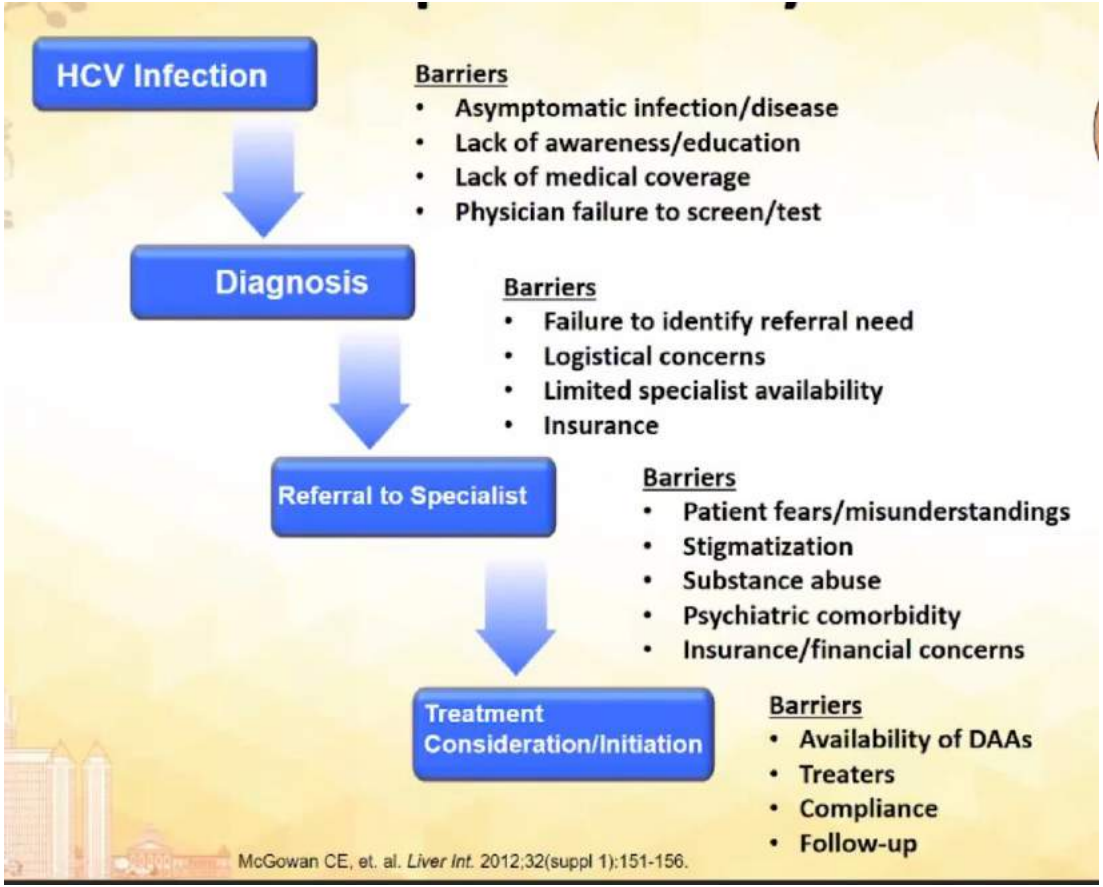
Key Takeaway:

Multiple barriers to the diagnosis, evaluation and delivery of hepatitis C treatment limit the widespread uptake of antiviral therapy.

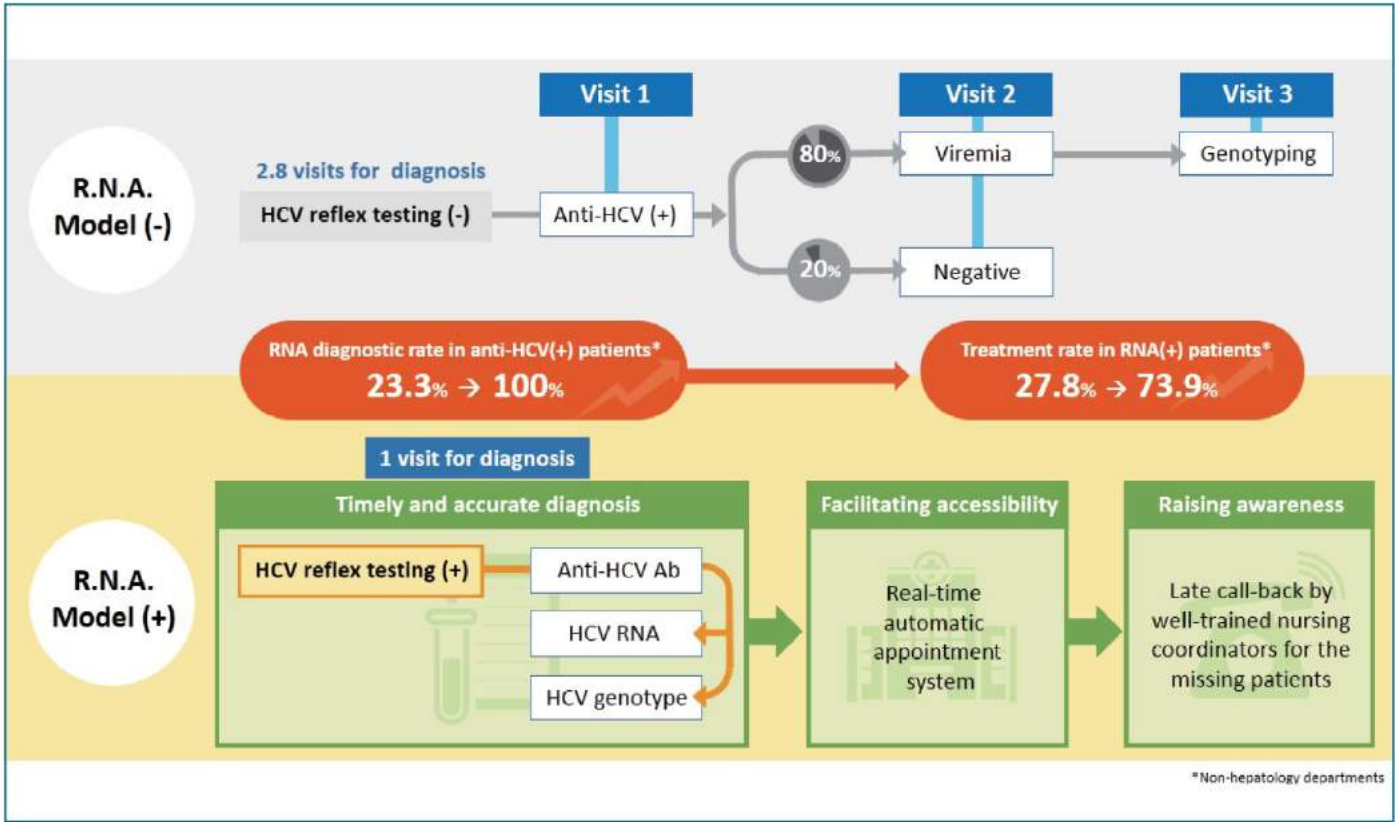
Recognizing the global burden of infection, there is a critical need to reduce current barriers to hepatitis C treatment.



Covid 19 slowed down elimination efforts globally.

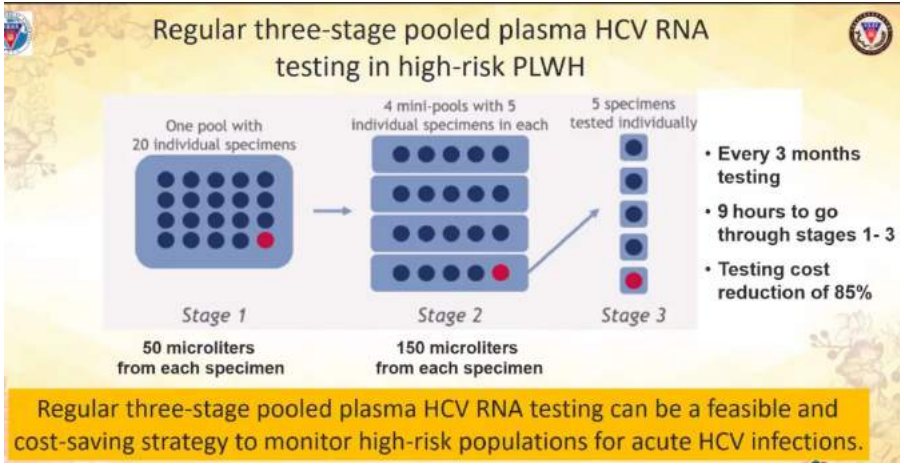


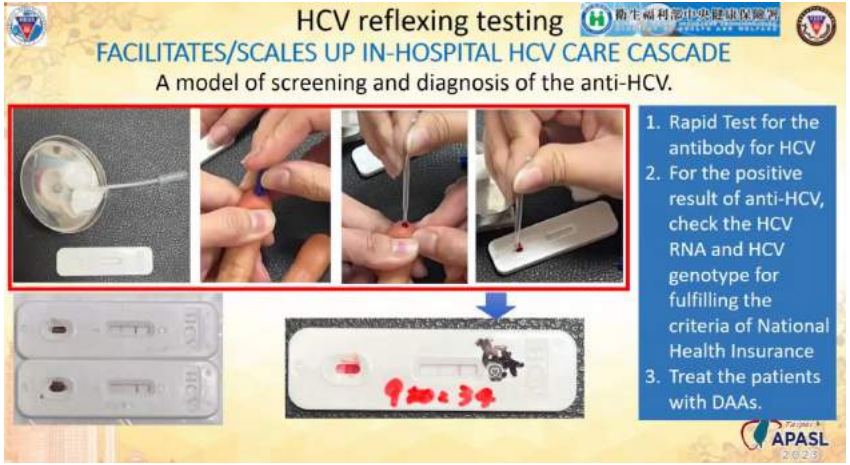
Scaling up the in-hospital hepatitis C virus care cascade in Taiwan



Key Takeaway: The application of the R.N.A. model significantly increased the in-hospital HCV treatment uptake rate from 6.4% to 73.9% for patients from non-hepatology departments

Scaling up diagnosis of hepatitis C virus in Taiwan





The performance and cost reductions of the pooled plasma HCV RNA testing strategy was evaluated by identifying acute HCV infections among people living with HIV (PLWH).

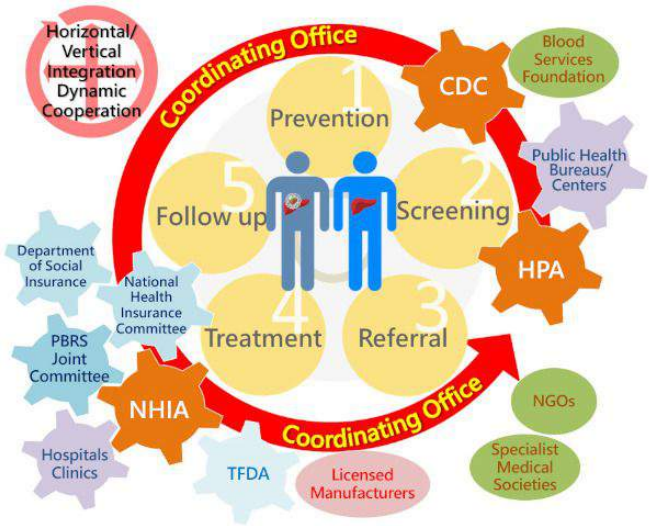
Three-stage pooled plasma HCV RNA testing successfully identified HCV viremia in high-risk PLWH with a testing cost reduction of 84.5%.

Key Takeaway: Timely and cost -effective diagnosis of hepatitis C virus (HCV) infection, leads to effective management which may prevent its transmission.

Sun, Hsin-Yun et al. “Three-Stage Pooled Plasma Hepatitis C Virus RNA Testing for the Identification of Acute HCV Infections in At-Risk Populations.” *Microbiology spectrum* vol. 10,3 (2022): e0243721. doi:10.1128/spectrum.02437-21

Scaling up public health efforts to eliminate Hep C in Taiwan

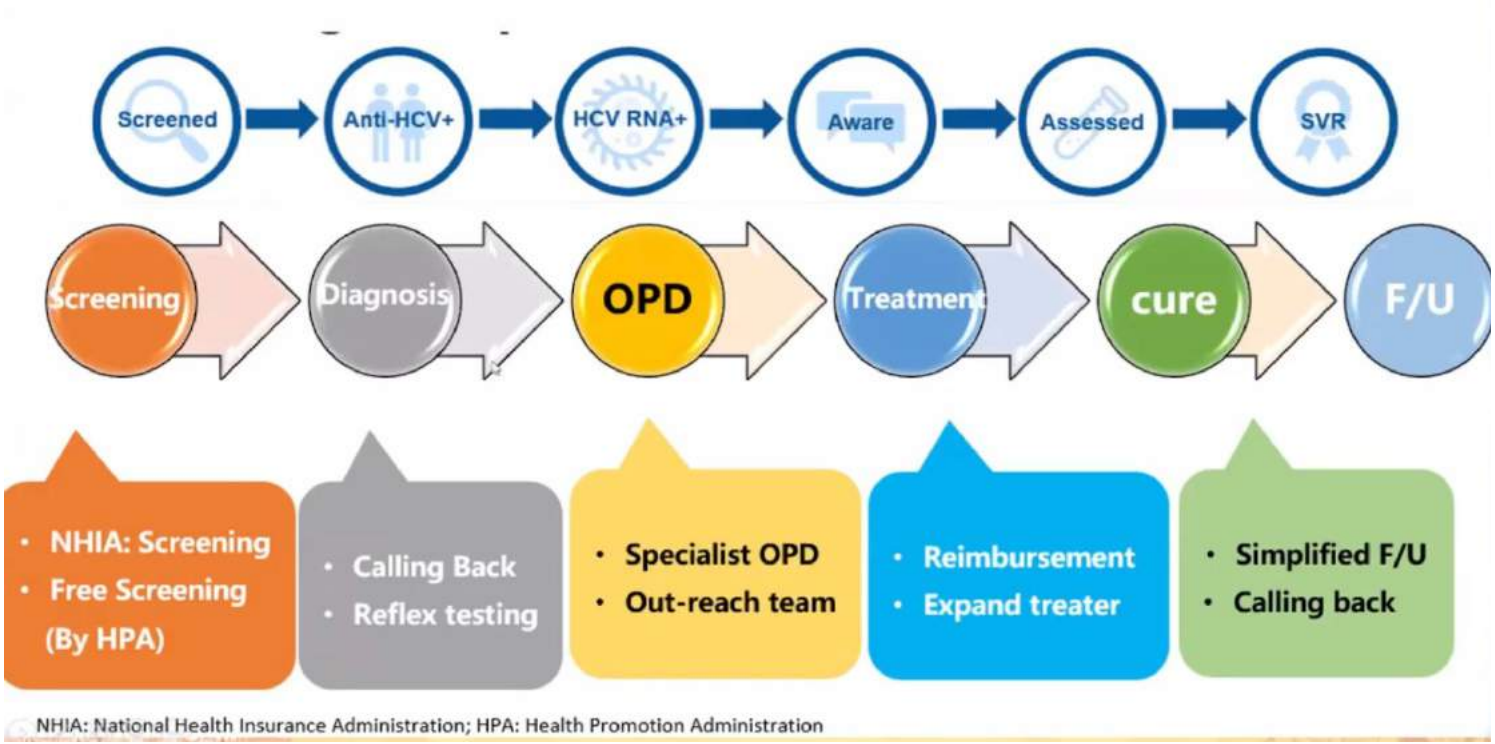
Taiwan Centers for Disease control instituted harm reduction programs and the NHCP office instituted monitoring, evaluation and micro-elimination. The NHCP office instituted monitoring, evaluation, micro-elimination and funding to linkage to care programs.



Key Takeaway: In addition to sustainable financing, it is imperative to scale-up screening coverage through a precision public health approach to fill the gap of under-diagnosis.

Chien, Nan, et al. "Taiwan Accelerates Its Efforts to Eliminate Hepatitis C." *Global Health & Medicine*, vol. 3, no. 5, 2021, pp. 293-300, https://doi.org/10.35772/ghm.2021.01064.

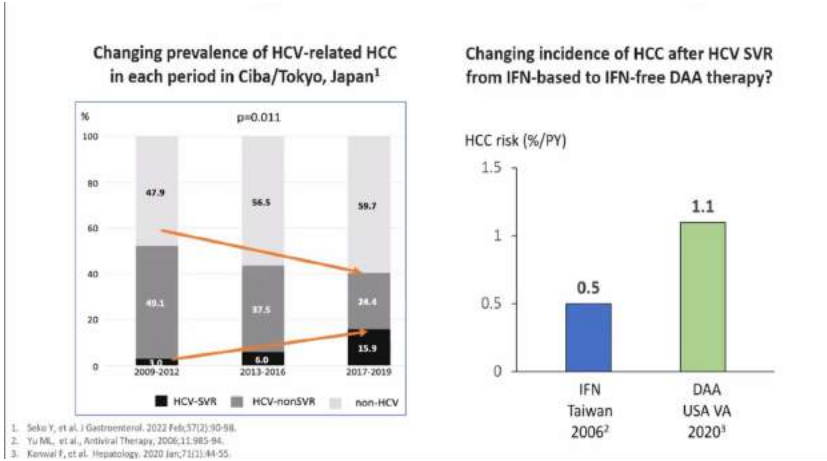
Summary of efforts achieve elimination goals



Key Takeaway: A multifactorial approach is required to overcome the barriers at every stage in the Hep C care cascade.

Surveillance of HCC in Patients With HCV After SVR

Prevalence of HCV-related HCC in the DAA era



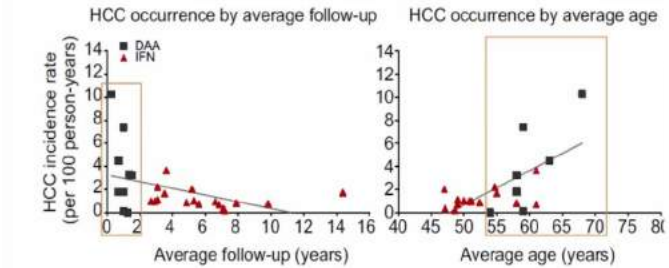


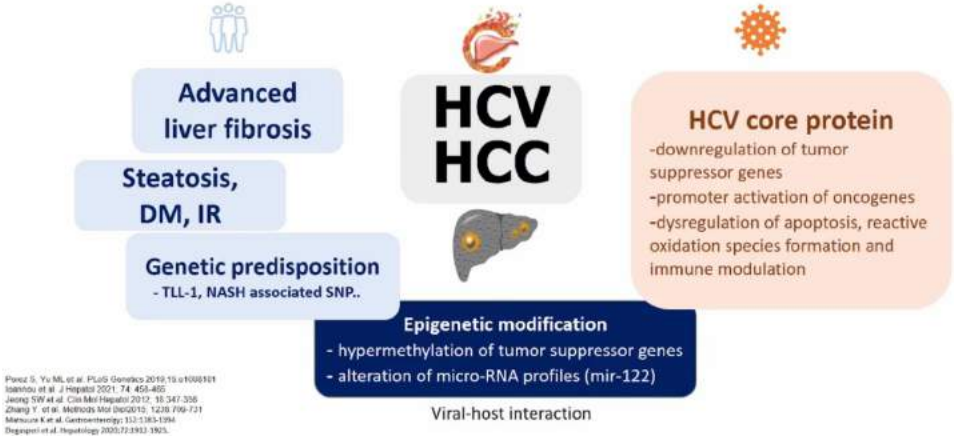
Table 3 Meta-regression analysis of factors associated with occurrence of hepatocellular carcinoma following HCV cure (Observations = 26).

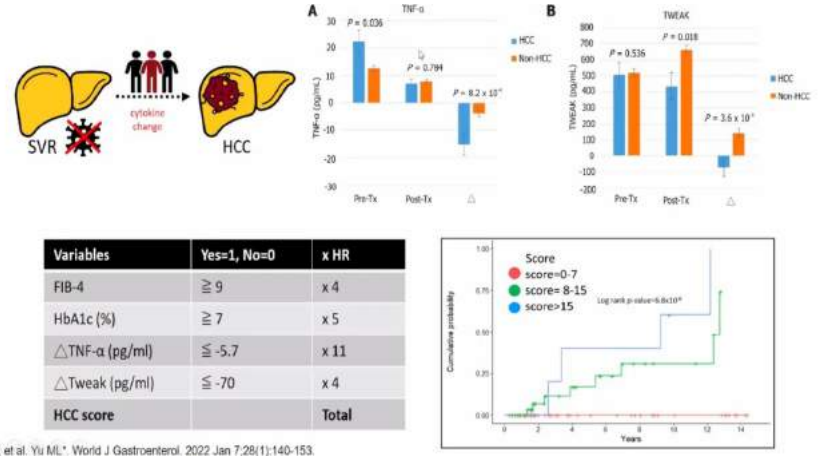
Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	p value	aRR	95% CI	p value
Treatment						
IFN	1.00	–	–	1.00	–	–
DAA	2.77	1.46–5.25	<0.01	0.68	0.18–2.55	0.56
Average follow-up, years	0.88	0.80–0.97	0.01	0.75	0.56–0.99	0.04
Average age	1.11	1.03–1.18	<0.01	1.06	0.99–1.14	0.12
Genotype 1	1.01	0.99–1.03	0.14	–	–	–

Wazry et al. J Hepatol 2017. 67: 1204-1212

Key takeaway: There is an increased risk of HCC post-SVR with DAA compared to IFN use. This may be attributed to aging and follow up duration. The antivirals did not contribute to the risk.

Why is there an increased association between HCV and HCC?





Variables	Yes=1, No=0	x HR
FIB-4	≧ 9	x 4
HbA1c (%)	≧ 7	x 5
△TNF-α (pg/ml)	≦ -5.7	x 11
△Tweak (pg/ml)	≦ -70	x 4
HCC score		Total

Lu MY, et al. Yu ML*. World J Gastroenterol. 2022 Jan 7;28(1):140-153.

The downregulation of TNF-α increases the risk of HCC among HCV patients following successful antiviral therapy. Inhibition of TNF-α may attenuate host immune surveillance against tumor cells

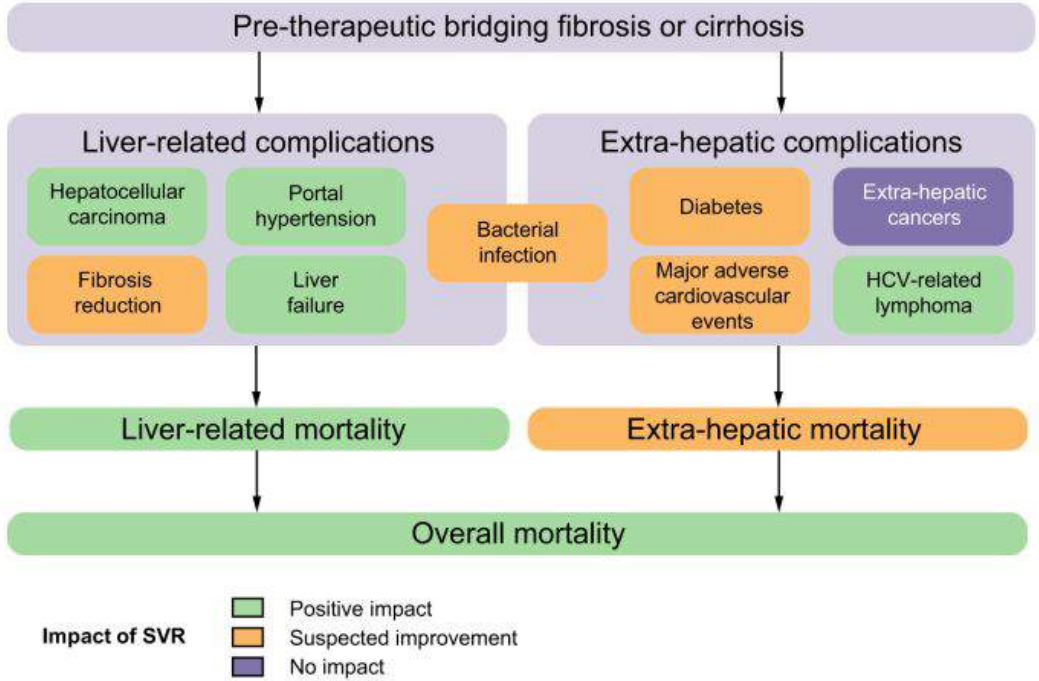
Key takeaway: The pathogenesis of HBV and HCV infections is generally immune-mediated, although these viruses have evolved multiple mechanisms to escape immune elimination and to continue replicating in an infected host for many years.

Which patients are at higher risk of HCC in HCV?

Risk at baseline

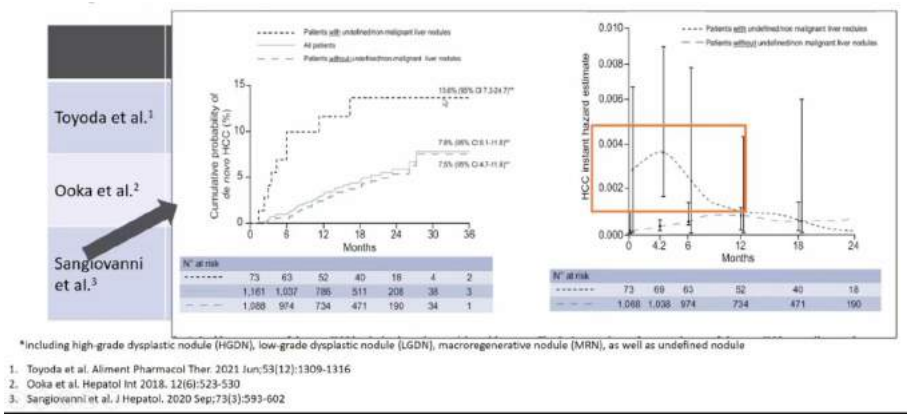
- –Non-characterized nodules
- –Significant liver diseases
  - –F3/4 (FIB-4 > 3.25)
  - –ALBI 2/3
  - –BL AFP ≥ 10 ng/mL
  - –BL rGT > 74 U/L
- –Risk genetic disposition
- –DM
- –Age

- **Risk after SVR**
  - –Advanced liver diseases after SVR
    - –F3/4 (FIB-4 > 3.25; APRI-M6 > 0.5)
    - –AFP-M6 ≥ 10 ng/mL
    - –ALT-M6
  - –uncontrolled DM



Key takeaway: HCC risk remains after HCV eradication due to irreversible epigenetic scars, unchangeable genetic predisposition, loss of immune surveillance and persistence unfavorable lifestyle/ environment

https://europepmc.org/article/pmc/7005771



*including high-grade dysplastic nodule (HGDN), low-grade dysplastic nodule (LGDN), macroregenerative nodule (MRN), as well as undefined nodule

1. Toyoda et al. Aliment Pharmacol Ther. 2021 Jun;53(12):1309-1316
2. Ooka et al. Hepatol Int 2018. 12(6):523-530
3. Sangiovanni et al. J Hepatol. 2020 Sep;73(3):593-602

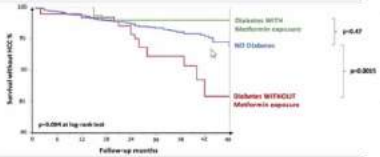
Risk with liver nodules (precancerous lesions)

A genetic risk score of hepatic fat accumulation, combining variants in 4 fatty liver associated genes was associated with de novo HCC among 509 cirrhotic patients after DAA SVR

- ***PNPLA3*** (patatin-like phospholipase domain containing 3)
- ***MBOAT7*** (membrane bound O-acyltransferase domain containing 7)
- ***TM6SF2*** (transmembrane 6 superfamily member 2)
- ***GCKR*** (glucokinase regulator)

Suggesting hepatic fat (i.e., lipotoxicity) promotes HCC after HCV cure

7,007 patients treated with DAA, of whom 97.7% achieved SVR (NAVIGATORE-Lombardia registry), 145 of 4,178 (3.5%) of patients with advanced fibrosis developed de novo HCC.



Suggesting diabetes increased risk of de novo HCC after HCV cure

Implications: Metabolic dysfunction associated fatty liver diseases (MAFLD) might play important role in hepatocarcinogenesis after HCV clearance by antiviral therapy

Degasperi E. et al. Hepatology. 2020 Dec;72(6):1912-23.

Valenti L. P. et al. Hepatol Commun. 2022 Apr;6(4):867-77.

Fibrosis-stage Specific Incidence of Hepatocellular Cancer after Hepatitis C Cure with Direct-Acting Antivirals:
A Systematic Review & Meta-Analysis

Clinical Gastroenterology and Hepatology

Pooled HCC incidence after SVR in patients with cirrhosis was very high (2.99/100 person-years) but may be declining as longer time accrues after SVR. In patients without cirrhosis, including F3 fibrosis, HCC incidence was lower than thresholds associated with cost-effective HCC screening.

Key Takeaway: Uncharacterized liver nodules and persistent advanced fibrosis are at high risk of HCC within the first three years after SVR.

Post SVR Screening Strategies

	APASL[1]	EASL[2]	AASLD[3]
Target population	All patients	F3, F4	F4
Screen Interval	**F0-2**: every 6 months for 2 years, then every 12 months **F3-4**: every 6 months	Every 6 months indefinitely	Every 6 months indefinitely
Modality	Sonography+ tumor markers (AFP, PIVKA-II, AFP-L3)	Sonography	Sonography with or without AFP

TASL[4] Consensus

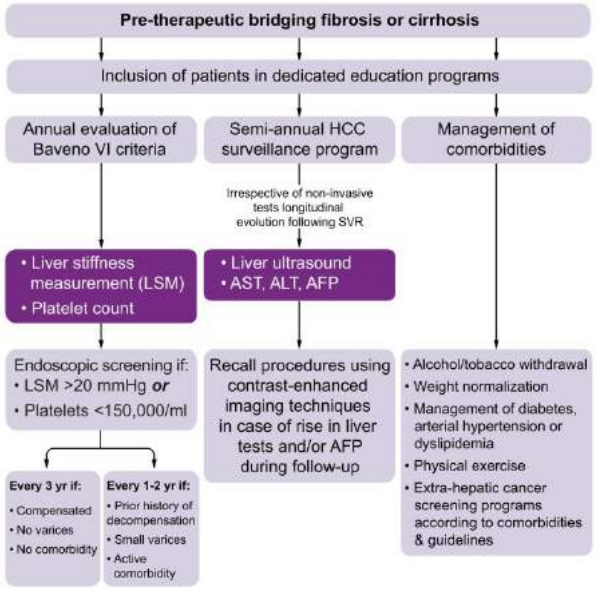
- ***For patients of F3-4 fibrosis, HCC surveillance with ultrasound is recommended at an interval of 3-6 months. (A1)***
- ***For patients of F2 fibrosis or with HCC risk factor(s), HCC surveillance with ultrasound is recommended at an interval of 6-12 months. (B1)***

- ✓ Advanced fibrosis
- ✓ Cirrhosis
- ✓ Past HCC history
- ✓ HBV/HCV coinfection
- ✓ Older age
- ✓ Male
- ✓ Dysplastic nodule
- ✓ Alcohol consumption
- ✓ DM
- ✓ Low albumin
- ✓ Low platelet count
- ✓ High AFP post-treatment
- ✓ High ALT post-treatment
- ✓ High γ-GT level

1.Hepatology International 2019; 13:649–661
2. J Hepatol 2020;73(5):1170-1218
3. https://www.hcvguidelines.org/
4. Yu ML, et al. J Formos Med Assoc. 2020

Implementing HCC surveillance in « apparently » low-risk patients?

Dropping surveillance in « apparently » high-risk patients?



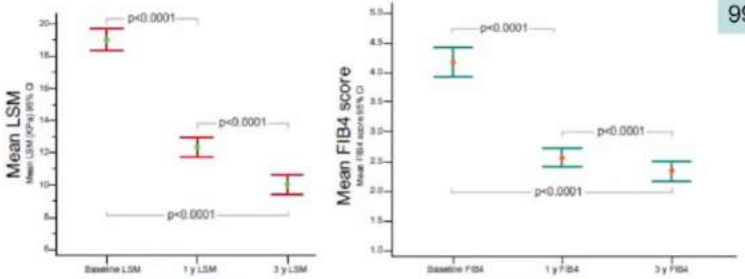
	EASL 2018	AASLD 2019
Pre-SVR F3 Fibrosis		
Definition	Histology LSM 10-13 kPa	NA
HCC surveillance	YES US every 6 months	NO
Pre-SVR F4 cirrhosis		
Definition	Histology LSM>13 kPa Fib-4>3.25 APRI>2	Histology LSM>12.5 kPa Fib-4>3.25 APRI>2
HCC surveillance	YES US every 6 months	YES US every 6 months ± AFP

A lifelong committment

Key Takeaway: HCC risk is one of the most important factors that should inform decisions of whether and how to screen for HCC. Promising strategies for estimating HCC risk include simplified scoring systems, sonographies, AFP, PICKA 2, AFP-L3, FIB 4, LSM (liver elastography) and multivariable HCC risk calculators.

Monitoring patients for HCC

Evolution of non-invasive tests



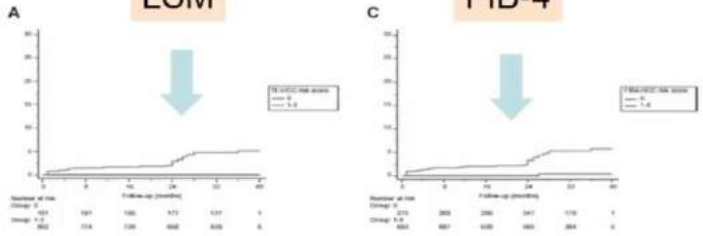
993 patients with HCV-cured ACLD

Alonso-Lopez et al, hepatology 2020

LSM

FIB-4

HCC risk

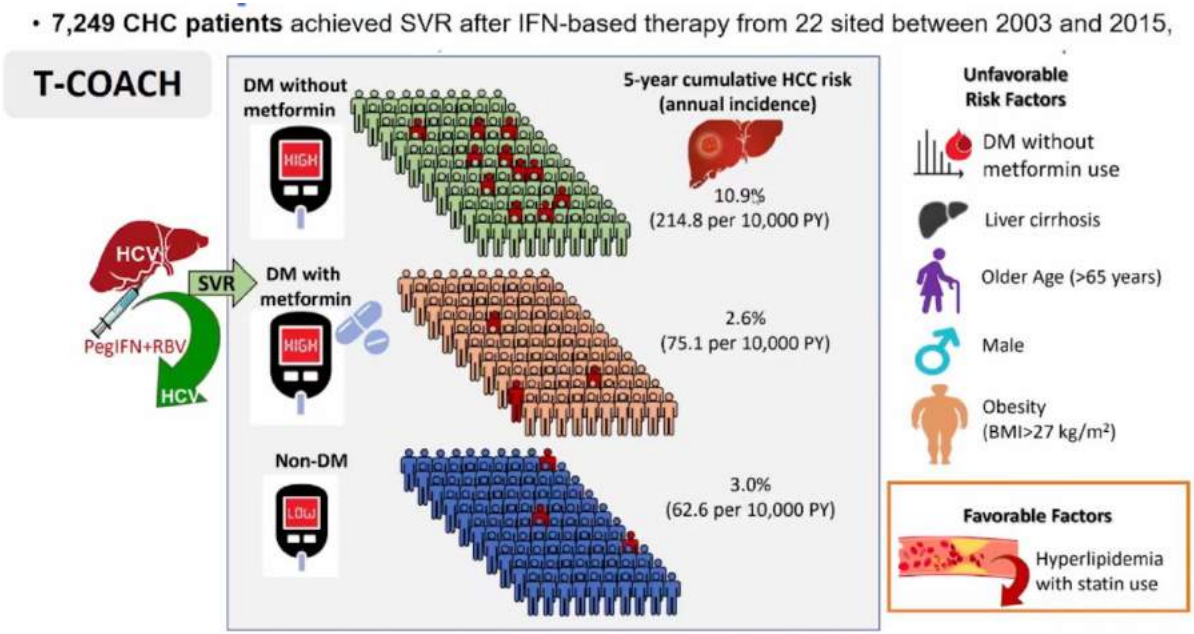


The TE-based HCC risk model predicted 0% of HCC occurrence at 3 years in patients with score 0 (baseline LSM ≤ 17.3 kPa, albumin >4.2 g/dL, and 1-year DeltaLSM > 25.5%) versus 5.2% in patients with score 1-3 (Harrell's C 0.779; log-rank 0.002). An alternative model with FIB-4 similarly predicted HCC risk.

Key takeaway: HCC risk persists in HCV SVR patients with baseline LC or high FIB 4 counts

https://pubmed.ncbi.nlm.nih.gov/33022803/

Chemoprevention of HCV-HCC after SVR



Tsai PC, et al., Yu ML*. J Hepatol. 2022 Oct 5:S0168-8278(22)03129-4.

Key takeaway: Metformin for DM patients and statins for hyperlipidemic patients could serve as chemopreventive agents for HCV patients after SVR.

Hepatitis B

This section contains the synopsis of the following sessions:

A. Asia Hepatitis Strategy Summit

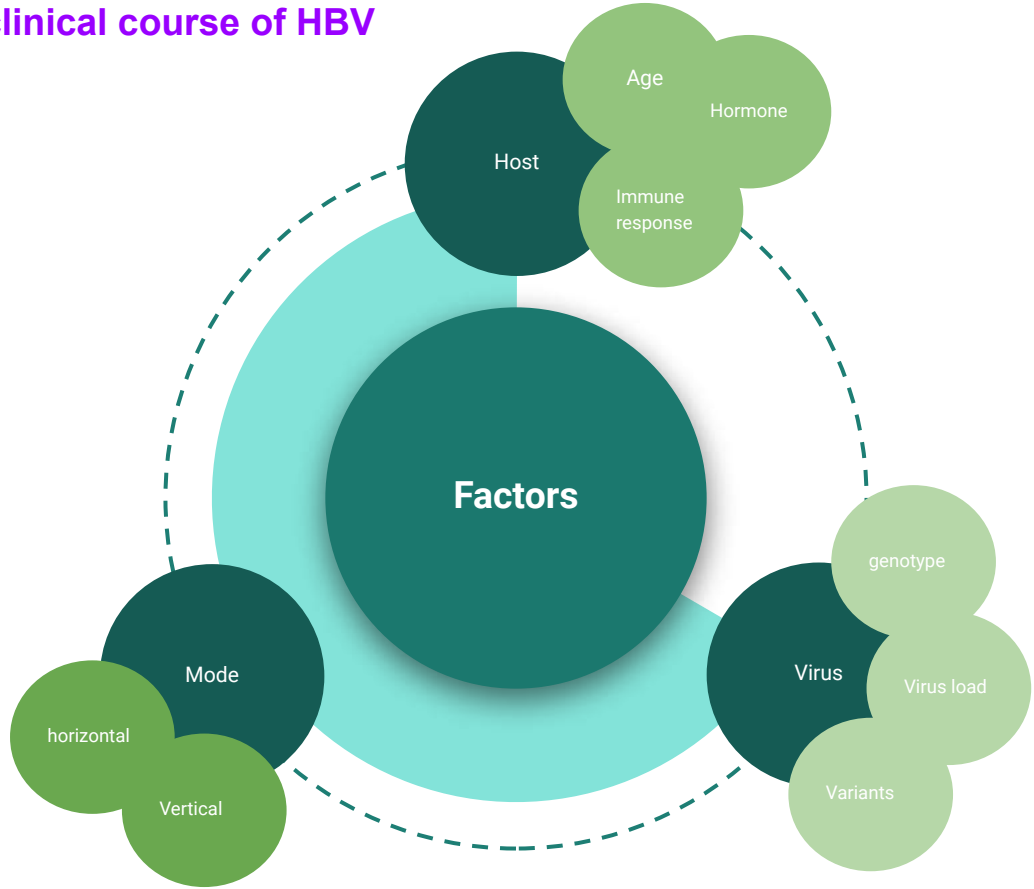
1. John Ward WHO'S Goal – GLOBAL PERSPECTIVE – WHO
2. Pei-Jer Chen Opening Remarks
3. Pei-Jer Chen- WHO Hepatitis Elimination Goal and Taiwan's Achievement

B. APASL Symposium 3-HBV: Prevention, Natural History, Current Therapy and Indication

1. Huey-Ling Chen Taipei Universal HBV Vaccination Program in Asian Pacific Region
2. Seng Gee Lim Singapore Hepatitis B Core Related Antigen (HBcrAg), Not as Good as It Seems?: A Critique and Systematic Review
3. Wen-Juei Jeng Taoyuan Stop-and-Watch Strategy in HBeAg-negative Off- Nuc Therapy
4. Pietro Lampertico Milan Stop-to-Cure Strategy in HBeAg-negative Off-Nuc Therapy

2 Symposiums = 7 lectures covered in 11 slides

Factors affecting the clinical course of HBV



Treatment Guidelines for Hep B

Professional Societies (AASLD[1], EASL[2], APASL[3,4])	World Health Organization (WHO[5])	
Guidelines more than 10 pages Very Complicated	Adults, adolescents and children with compensated or decompensated **cirrhosis**	Adults without cirrhosis, **> 30 years old** (in particular), and have **persistently abnormal ALT levels** and **HBV DNA >20,000 IU/mL**

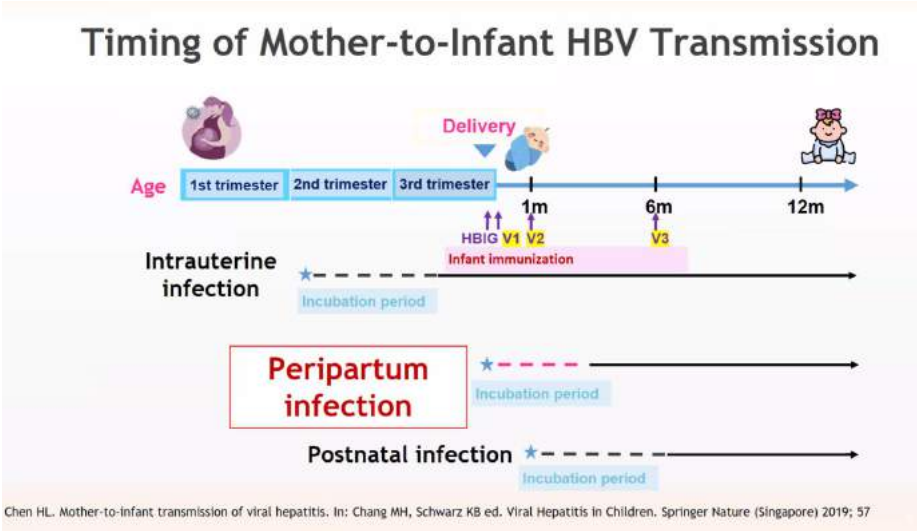
1. Terrault NA, et al. *Hepatology*. 2018;67:1560-1599. 2. EASL. *J Hepatol*. 2017;67:270-398. 3. Sarin SK, et al. *Hepatol Int*. 2016;10:1-98. 4. Gane EJ, et al. *J Viral Hepat*. 2020;27:466-475.
5. WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015.http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_en

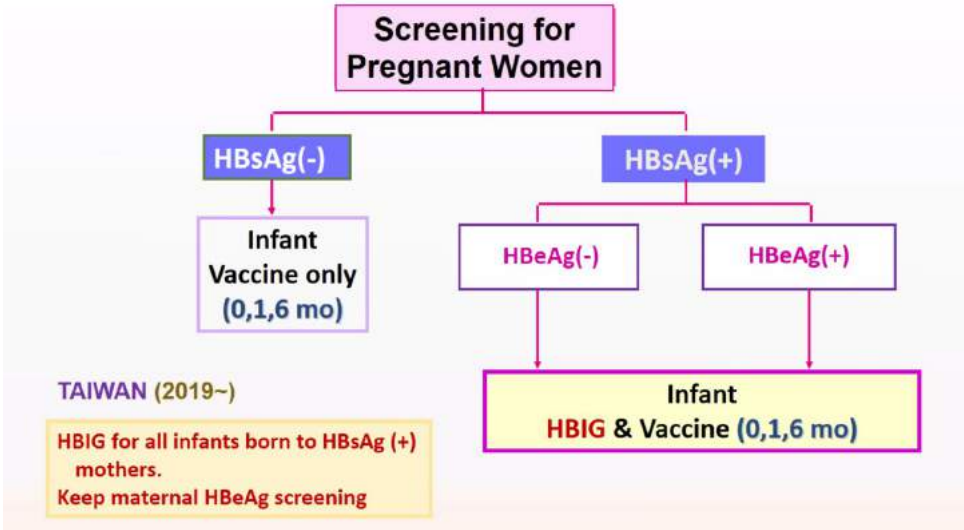
Key Takeaway: WHO is updating their HBV diagnosis and treatment guidelines so that they are simplified for LMICs.

Key recommendations:

- Noninvasive assessment of liver disease (e.g APRI, Fib-4)
- Treat all with clinical evidence of compensated or decompensated cirrhosis
- Treat persons > 30 years old (in particular), who have persistently abnormal ALT levels and high HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status
- If HBV DNA testing is not available, treatment considerations can be based on persistently abnormal ALT levels alone regardless of HBeAg status

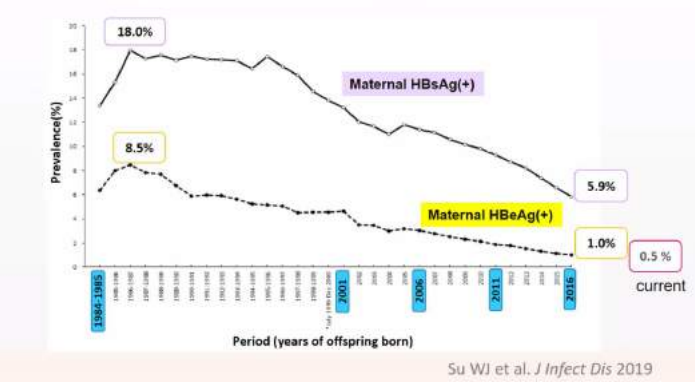
Immunization and Screening to Prevent Mother to Infant Transmission of HBV





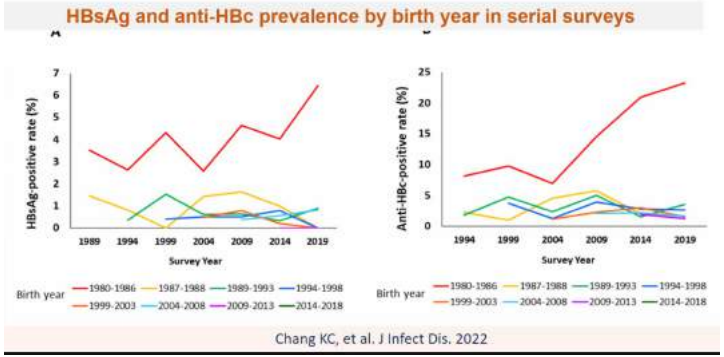
Key Takeaway: Taiwan's updated vaccination strategies include maternal screening and offers HBIG to all infants born to HBsAg + mothers, at birth

Effect of universal vaccination programs on HBV infections and transmissions



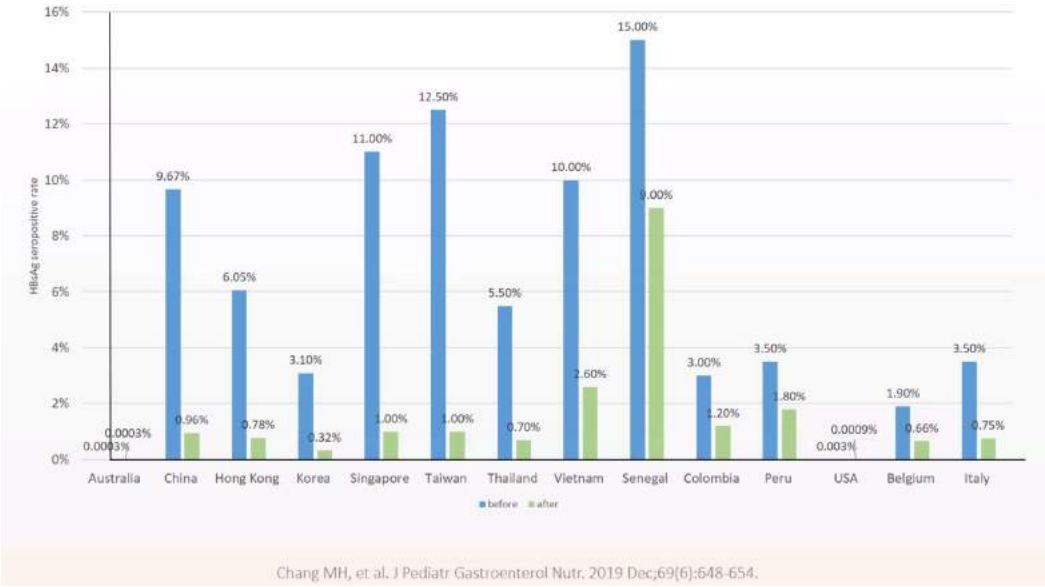
Su WJ et al. *J Infect Dis* 2019

Rates of maternal HBsaG and HBeAg positivity declined with vaccination programs



Chang KC, et al. J Infect Dis. 2022

Neonatal vaccination also reduced horizontal infection



Chang MH, et al. J Pediatr Gastroenterol Nutr. 2019 Dec;69(6):648-654.

Change in HBsAg positivity, before and after implementation of vaccination programs in different countries.

Key Takeaway: Vaccination programs have decreased HBV positivity rate when implemented.

Key Takeaways

- In spite of successful vaccination efforts, adequate neonatal immunization cannot totally prevent mother to infant transmission as breakthrough infections due to vaccine failure still occur.[1]
- The higher the maternal HBV DNA the higher the infant HBSAG positive rates [1]
- Maternal TDF treatments can reduce infant sag positive rates at 6 months and 12 months [2]
- APASL 2014 guidelines[3] suggest starting AVT at 28-32 weeks gestational age and stopping it at birth if the HBsaG + MOTHER HAS A VIRAL load of >10^7
- Tenofovir or telbivudine are the drugs of choice
- APASL 2022 guidelines[3] suggest starting AVT once the maternal load is >2x10^5 or the mother is HBeAg +
- Long-term safety studies on the growth and bone development of HBV-infected mothers with and without fetal exposure to TDF show no difference between children in the 2 groups, even after 2-7 years of follow-up after birth.[4]
- World Health Organization 2020 Guideline on antiviral prophylaxis in Pregnancy recommends [5]

1. Pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥ 5.3 log10 IU/mL (≥ 200,000 IU/mL) receive tenofovir prophylaxis from 28 weeks until at least at birth
2. In settings where antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative.

1. Wen WH et al JHepatol 2013
2. Chang KC et al AP&T 2019
3. Chen HL et al J Infect Dis 2018
4. Wen WH et al J Hepatol 2020;72:1082-1087
5. https://www.imrpress.com/journal/CEOG/48/1/10.31083/j.ceog.2021.01.2240/

Novel Biomarkers to diagnose HBV - HBcrAg

Biomarkers used for screening and diagnosis:

- HBsAg
- HBV- RNA
- HBV- DNA
- HBcrAg

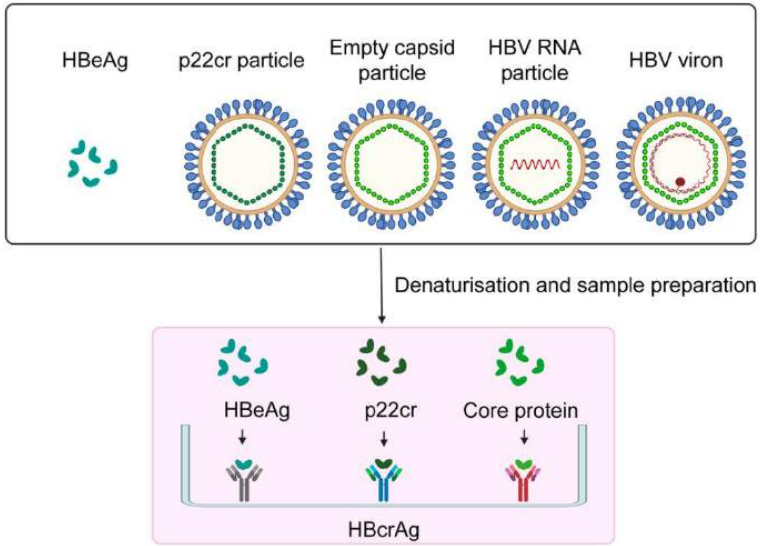
Endpoints evaluated:

- Predicting HBeAg seroconversion
- Predicting HBsAg loss
- Predicting treatment responses during antiviral therapy
- Predicting HBV flares when stopping NA therapy
- Predicting phases of CHB

HBV biomarkers are useful mainly for HBV events not liver events (like liver cancer, failure, cirrhosis or mortality).

The biological pathway of HBcrAg is distinct to that of HBsAg and are translation products from precore and pregenomic RNA comprising HBV core antigen, p22cr and HBeAg.

Key takeaway: Novel biomarkers like HBcrAg show potential in diagnosis of HBV and prognosis during treatment.



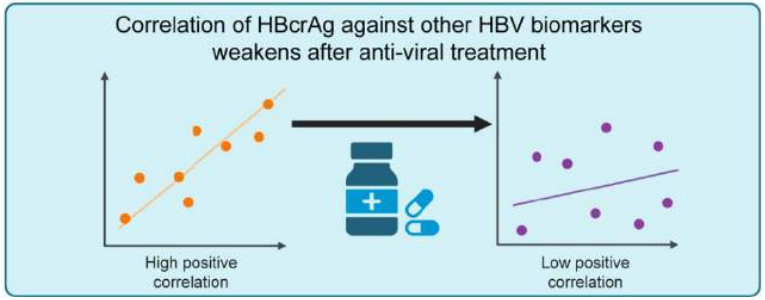
In HBeAg (+) patients, Envelope aG IS ~70% of HBcrAg BUT HBeAg (-) patients, other components are not quantifiable.

Using HBcrAg as a predicator for:

HBeAg seroconversion (6 studies; median AUROC 0.860)	Treatment response (8 studies; median AUROC 0.757)
HBsAg loss (6 studies; median AUROC 0.645)	Relapse after treatment cessation (8 studies; median AUROC 0.688)

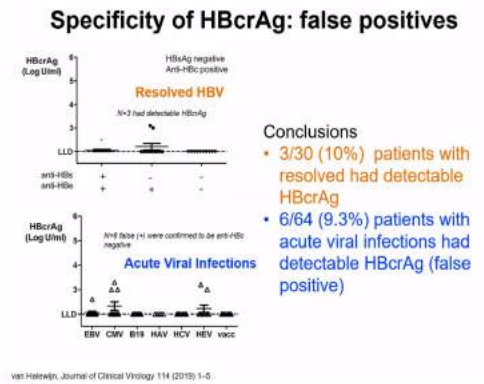
Hong X et al J Virol 2021; 95 (3):e01695-20
Adraneda et al, J Hepatol 2022

Utility of HBcrAg

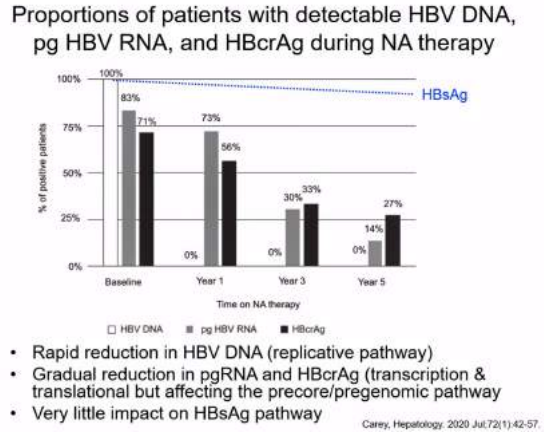


Predictor (AUROC)			Correlation of HBcrAg		
HBeAg seroconversion	0.860	Excellent	To HBV DNA	0.630	Strong
HBeAg negative CHB infection	0.867	Excellent	HBV RNA	0.619	Strong
Treatment response	0.757	Good	cccDNA	0.550	Strong
Relapse after stopping therapy	0.688	Poor	qHBsAg	0.414	Weak
HBsAg loss	0.645	Poor	After antiretroviral treatment		Decreased

Key takeaway: Timely and accurate Interpretation of HBcrAg is essential to optimize its use as a biomarker for HBV



Studies show a false positivity rate of 9.3% and false negative rate of 12-35%



Adraneda, Celina et al. “A critique and systematic review of the clinical utility of hepatitis B core-related antigen.” *Journal of hepatology* vol. 78,4 (2023): 731-741.

PANEL DISCUSSION

Challenges Faced in Hep B Elimination

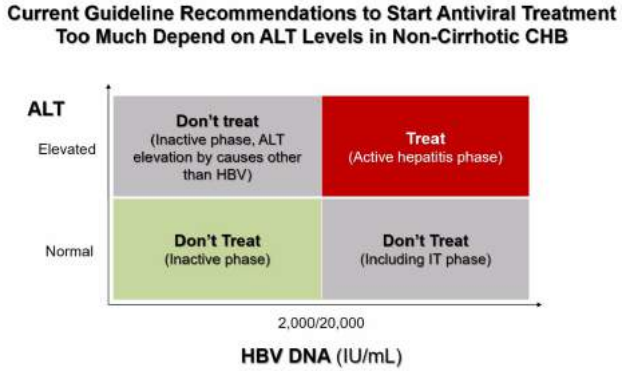
- Need to involve non-specialists in care cascade
- Guidelines from multiple professional societies are long and complicated
- Care delivery is not decentralized
- Low cure rate with currently available treatments

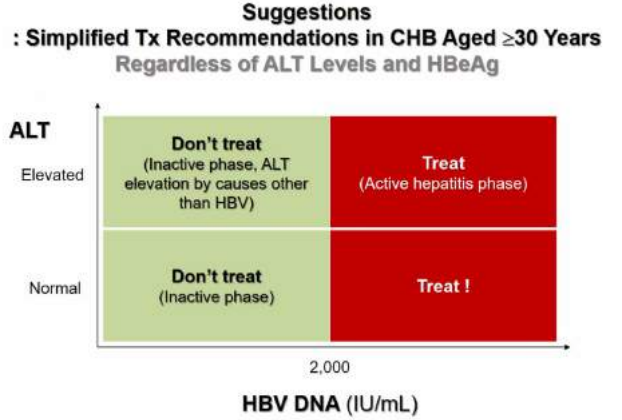
Strategies employed for Hep B Control

1. **Primary prevention** through widespread vaccination programs show good results (especially in decreasing maternal-fetal transmission)

2. **Secondary prevention** through initiating treatment at the OPTIMAL time, can improve prognosis.
- HBV integration and clonal hepatocyte expansion occurs at early stages of the infection
- Normal ALT levels do not necessarily reflect a normal liver
- Identification and treatment of patients in “grey zones”can reduce fibrosis and progression of disease
- Simplification of guidelines can lead to expansion of treatment criteria
- Suggestion: To initiate drug therapy EARLIER in patients not usually recommended for treatment can control HBV with improved cost-effectiveness

3. **Tertiary prevention** through antiviral treatments can reduce incidence of HBV related HCC.



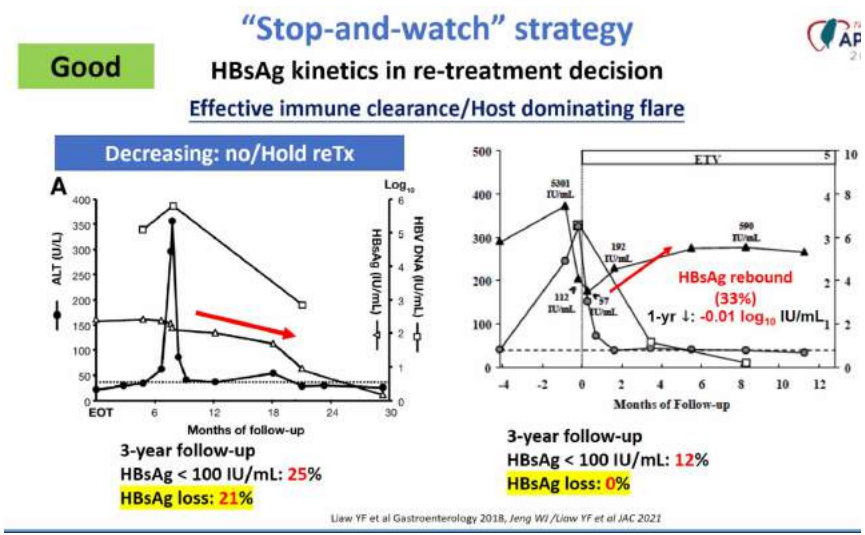


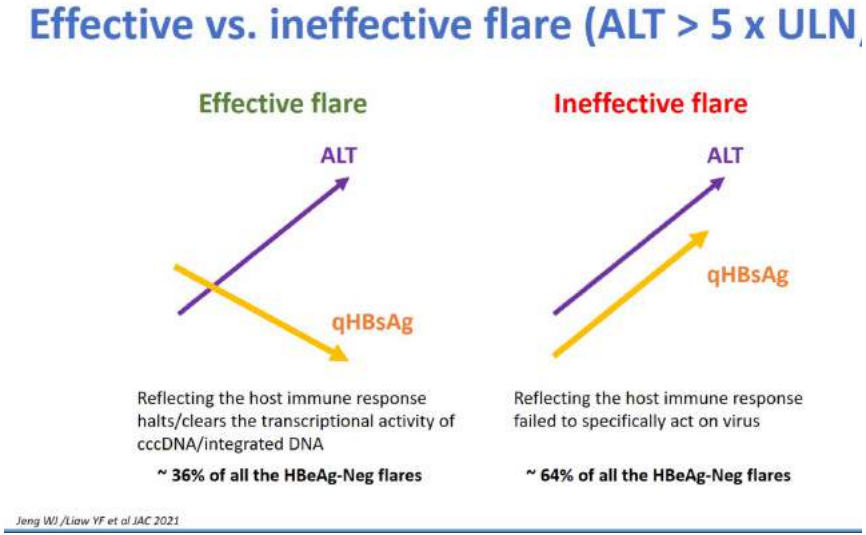
Stop-and-Watch Strategy in HBeAg-negative Off- Nuc Therapy

The risks and benefits of a finite versus an infinite treatment should be discussed with patients.

Benefits: Increased HBsAg loss, may decrease HCC, no need to take medications lifelong, adherence issues are resolved

Risk: Need for stringent follow up, may encounter a flare (ALT >5X ULN)

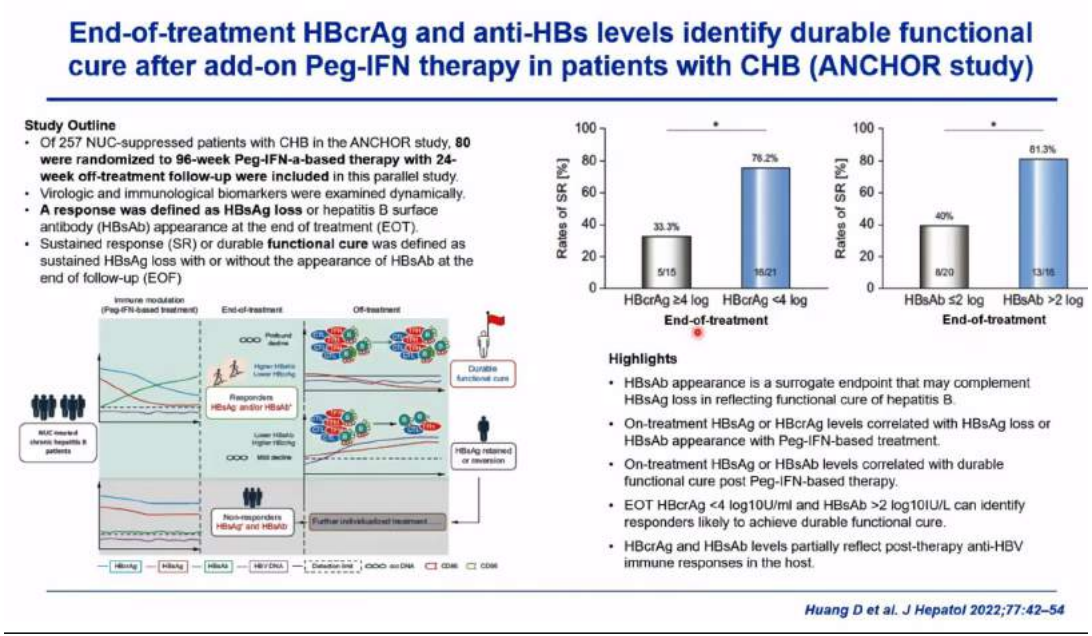




Key Takeaway: Approaching a flare: Kinetics of HBsAg helps to differentiate effective from ineffective flares. It can help stimulate close monitoring for those with effective flares and consider retreating in those with ineffective flares.

Stop-to-Cure Strategy in HBeAg-negative Off-Nuc Therapy

- In selected non-cirrhotic HBeAg (-) patients, discontinuation of NUC before HBsAg loss is possible.
- BUT it has to be used very carefully as a therapeutic option, keeping in mind endpoints, predictors, ALT flares, retreatment and compliance.
- Studies suggest that the probability of achieving HBsAg loss off therapy correlates with age at NUC start (before 40), HBsAg levels at EOT and duration of NUC therapy (>3.5 years)
- Add on therapeutics may lead to 10-30% HBsAg loss in NUC suppressed.



Key Takeaway:

EOT HBsAg levels are the best predictors (Caucasian vs Asian), and the role of new HBV biomarkers should be elucidated.

Safety of NUC discontinuation before HBsAg loss should be considered.

Advances in HCC

Prevalence, Diagnosis and Management

Please note: The flow of content has been modified to make up for the disconnected flow of the speaker sessions.

This section contains the synopsis of the following sessions:

1. **APASL Symposium 26-HCC/CC: Basic Science and Biomarkers (5 lectures)**

Moderators: Sheng-Nan Lu (Kaohsiung) / Osamu Yokosuka (Chiba)

1. Xin Wei Wang (Bethesda) Evolution of Cell Composition During Hepatocellular Carcinoma Progression and Treatment
2. Irene Oi-Lin Ng (Hong Kong) The Evolution of Hepatocellular Carcinoma at Single Cell Level
3. Shiou-Hwei Yeh (Taipei) Human Genomic HBV in Hepatocarcinogenesis and Diagnosis Human Genomic HBV in
4. Hepatocarcinogenesis and Diagnosis
5. Stephanie Ma (Hong Kong) Genetically Defined, Syngeneic Organoid Platform for Understanding Heterogeneity and Response to Therapy in Liver Cancer

2. **APASL Symposium 30-HCC/CC: Systemic Therapy Including Early Phase Data for Novel Treatments in HCC (5 lectures)**

Moderator: Sheng-Nan Lu (Kaohsiung) / Yi-Hsiang Huang (Taipei)

1. Stephen Lam Chan (Hong Kong) Changing Landscape of Systemic Therapy for Unresectable HCC
2. Valerie Chew (Singapore) Understanding Immunobiology of Hepatocellular Carcinoma for Biomarkers and Therapeutic Discovery
3. Tim Greten (Bethesda) Immune-Related Biomarkers for Systemic Therapy of HCC
4. Bruno Sangro (Pamplona) Systemic Therapy for HCC: From Guidelines to the Real World (Western Perspective)
5. Yi-Hsiang Huang (Taipei)Systemic Therapy for HCC: From Guidelines to the Real World (Asian Perspective)

3. Masatoshi Kudo (Osaka) Novel Treatment Strategy in Intermediate-Stage HCC (1 lecture)

3 symposiums = 11 lectures/talks covered in 18 slides

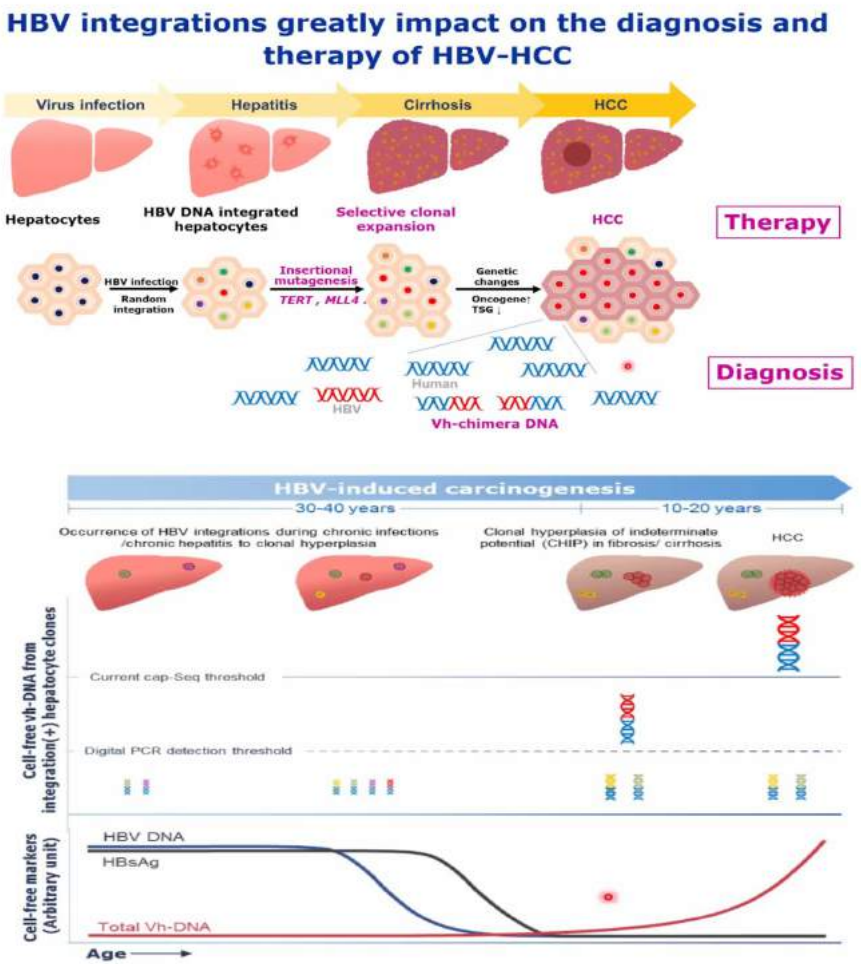
Epidemiology of HCC

- Also called primary liver cancer (PLC)
- Top 5 lethal cancers in the world
- Mortality >830,000 (8.3%)
- Disproportionately affects people in SE Asia and Africa
- Male/ female ratio- >3:1

Human Genomic HBV in Hepatocarcinogenesis and Diagnosis

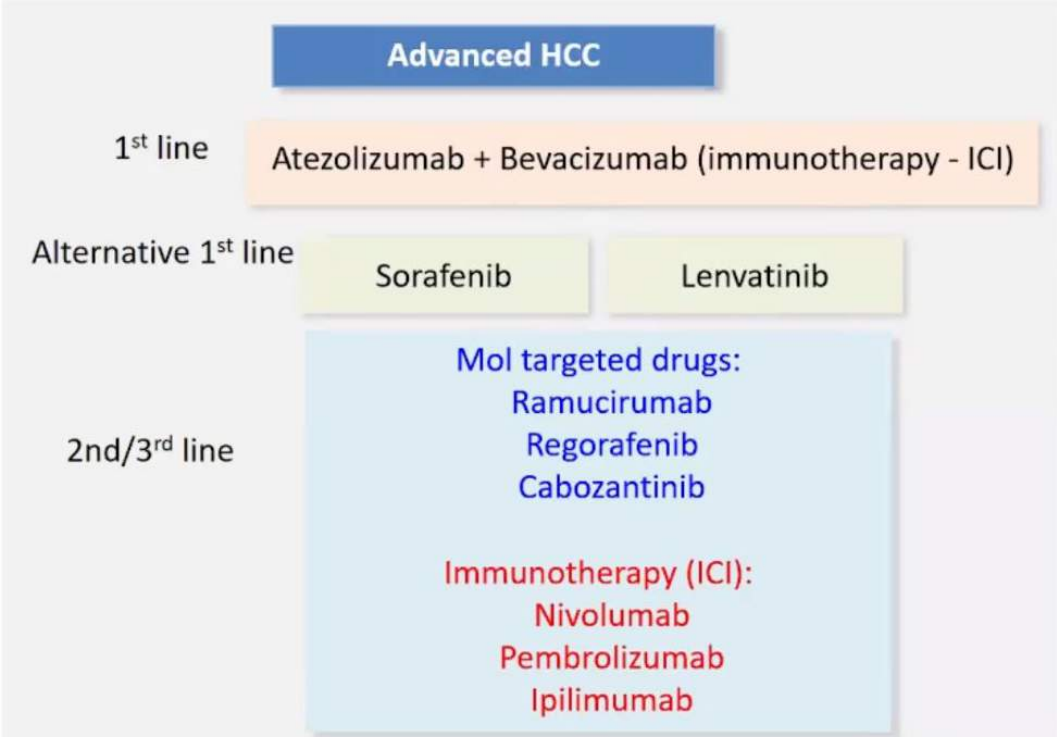
- Infection by HBV is the main risk factor for hepatocellular carcinoma (HCC) worldwide.
- HBV directly drives carcinogenesis through integrations in the human genome.
- Integration of viral enhancer nearby a cancer-driver gene may lead to a strong overexpression of oncogenes.

Key takeaway: HBV integrations have direct clinical implications as HCC with a high number of insertions develop in young patients and have a poor prognosis.



Approach to Treatment

- Usually diagnosed late; 80% are inoperable
- High recurrence rate even after surgery
- Resistant to conventional chemotherapy
- Drugs are given with a “one size fits all” approach
- Molecularly targeted drugs have modest effects
- The of tumor microenvironment of HCCs can limit the effectiveness of immunotherapy



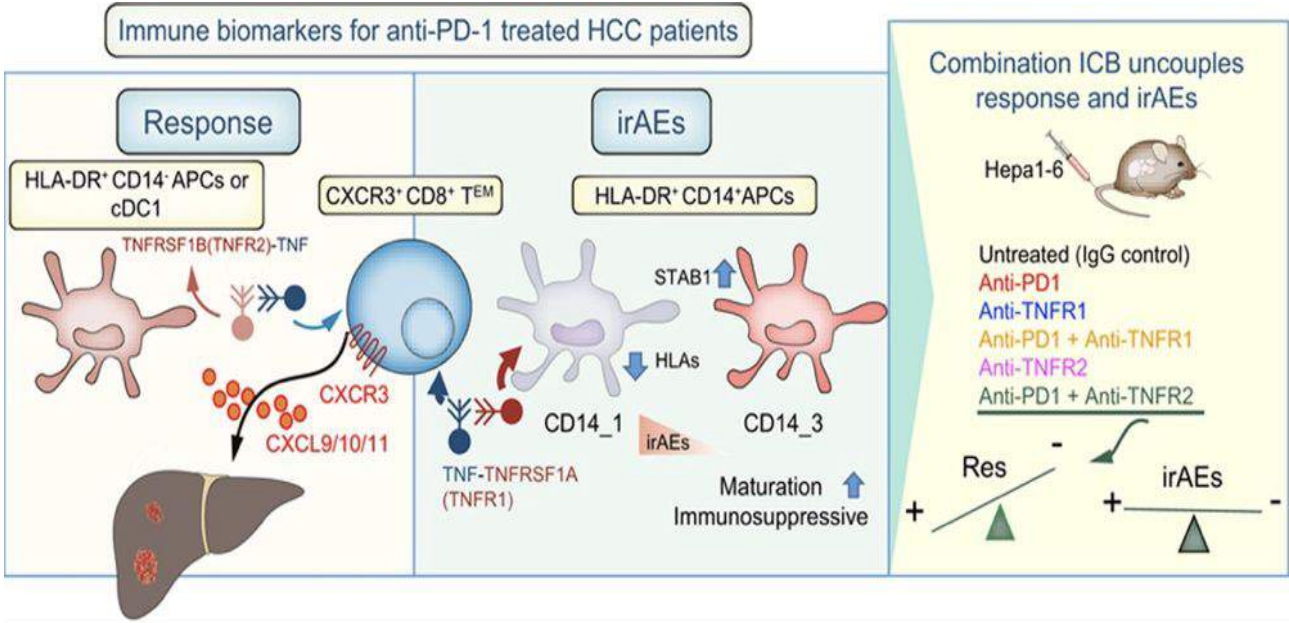
Current regimens for treatment of HCC

Key Takeaway:

- HCC heterogeneity (intra and inter tumoral) is a big challenge for precision medicine
- Better knowledge of the molecular landscape and tumor microenvironment (TME) is needed.

Understanding Immunobiology of Hepatocellular Carcinoma for Biomarkers and Therapeutic Discovery

- Response rates to immune checkpoint blockade (ICB) treatment in HCC remain modest and adverse events are common.
- Researchers identified early predictors of response and gained an in-depth understanding of the immunological mechanisms behind response and adverse events in patients with HCC treated with ICB.
- Peripheral biomarkers like anti-PD-1 can be used to predict response to therapy.
- Antigen-presenting cells and CD8 TEM cell function act as an interface between response and toxicity.
- TNFR2 inhibition uncouples response and toxicity in anti-PD-1 immunotherapy.



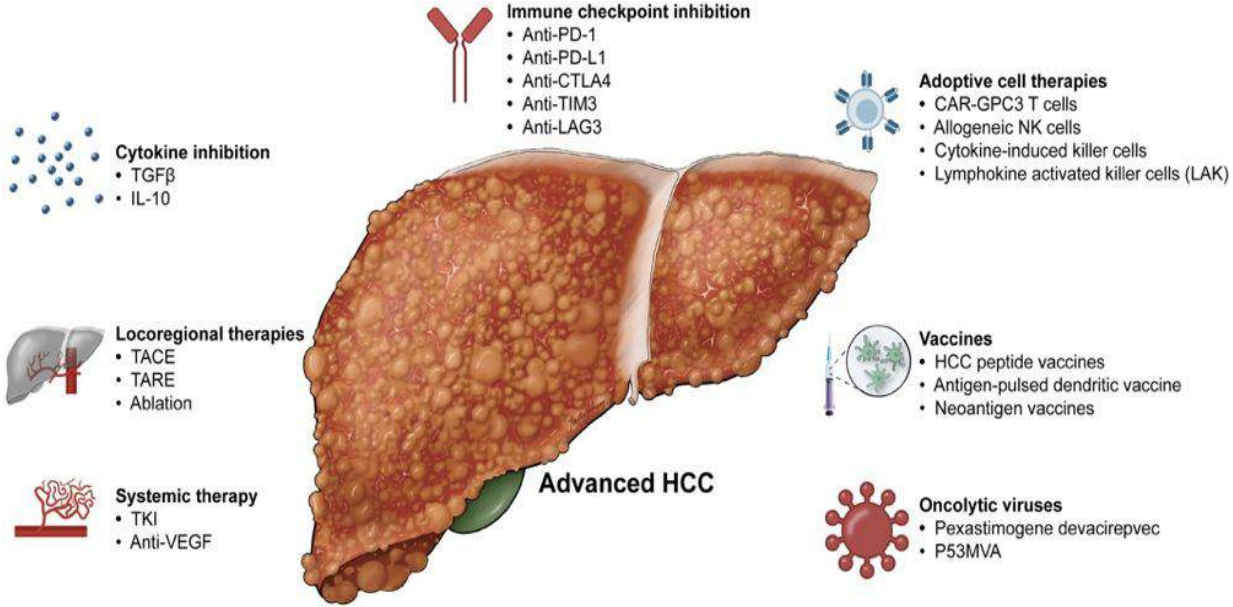
Key Takeaway - A new combination immunotherapy for HCC - Anti-PD-1 + anti- TNFR2 was proposed which shows enhanced response without increased adverse reactions.

Chuah S, Lee J, Song Y, et al. Uncoupling immune trajectories of response and adverse events from anti-PD-1 immunotherapy in hepatocellular carcinoma. *J Hepatol*. 2022;77(3):683-694. doi:10.1016/j.jhep.2022.03.039

Changing Landscape of Systemic Therapy for Unresectable HCC

Current treatment guidelines

- Patients suitable for immunotherapy or BeV - A +T or STRIDE -> TKI
- Patient unsuitable for immunotherapy or BeV- TKI sequence

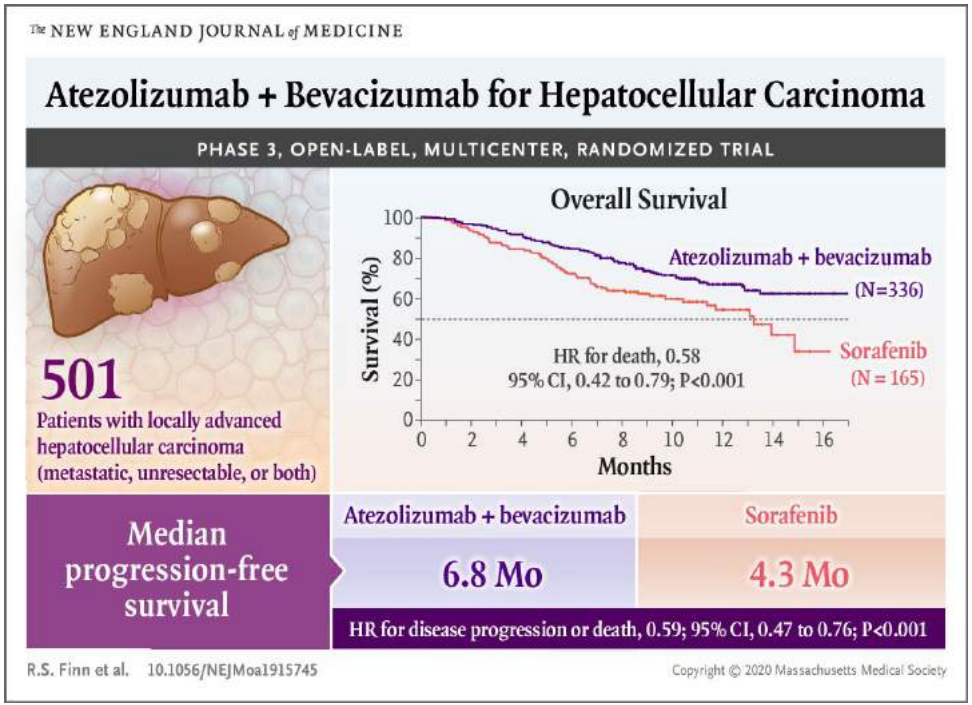


Key takeaway

- Systemic therapy has moved from monotherapy small molecules to a sequence of combinational treatments consisting of targeted agents and immunotherapy.
- Systemic therapy will be expanded to early and intermediate stage HCC.

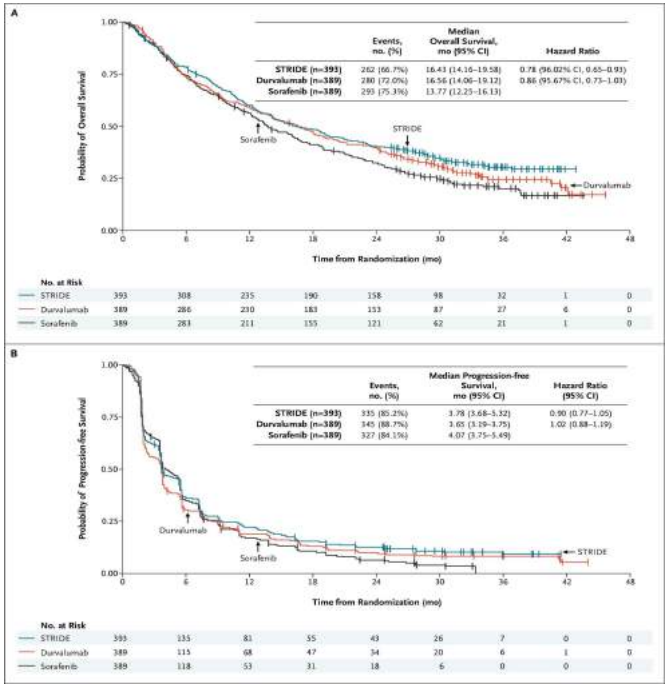
Foerster, F, Gairing, SJ, Ilyas, SI, Galle, PR. Emerging immunotherapy for HCC: A guide for hepatologists. *Hepatology*. 2022; 75: 1604– 1626. https://doi.org/10.1002/hep.32447

Advanced Immunotherapy used in the Treatment of HCC



A single, high priming dose of tremelimumab plus durvalumab (an infusion regimen termed STRIDE - Single Tremelimumab Regular Interval Durvalumab) showed encouraging clinical activity and safety in a phase 2 trial of unresectable hepatocellular carcinoma.

- STRIDE significantly improved overall survival versus sorafenib.
- Durvalumab monotherapy was noninferior to sorafenib



Kaplan–Meier Estimates of Overall Survival and Progression-Free Survival in the Intent-to-Treat Population

Key takeaway and Treatment implications:
In patients with unresectable hepatocellular carcinoma, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib.

Novel Immune-Related Biomarkers for Systemic Therapy of HCC

Innate lymphoid cells (ILCs)

- Contribute to immunosurveillance in cancers
- Have pro and anti-tumor properties depending on their environments
- Interact with other immune cells by secretion of cytokines, thus shaping the TME.

Using flow cytometry and single-cell sequencing, researchers characterized ILCs in the peripheral blood (PB) of HCC patients at baseline and after treatment with immune checkpoint inhibitors (ICI).

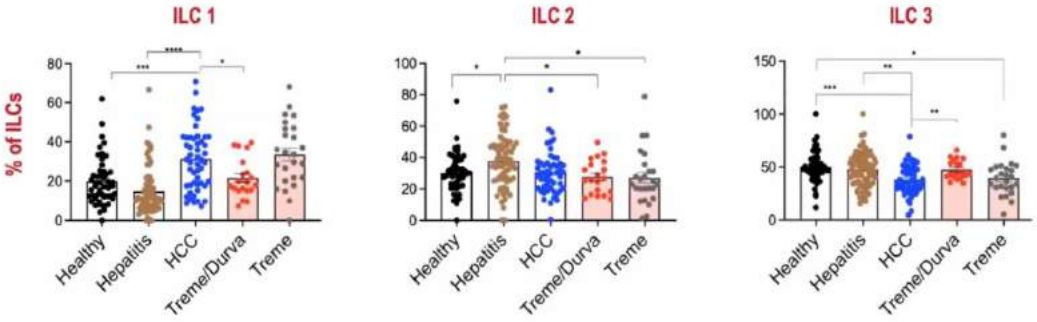
Characterization of ILC subsets showed

- a significant increase in ILC1
- a decrease in ILC3
- a subgroup of NK-like ILCs expressing cytotoxicity markers and NKp80/*KLRF1*.

a. These cells showed low abundance in patients with HCC and were enhanced after combined anti-CTLA-4 and anti-PD-1 immunotherapy.

b. The transcriptomic signature of these cells was associated with better progression-free survival in large HCC cohorts.

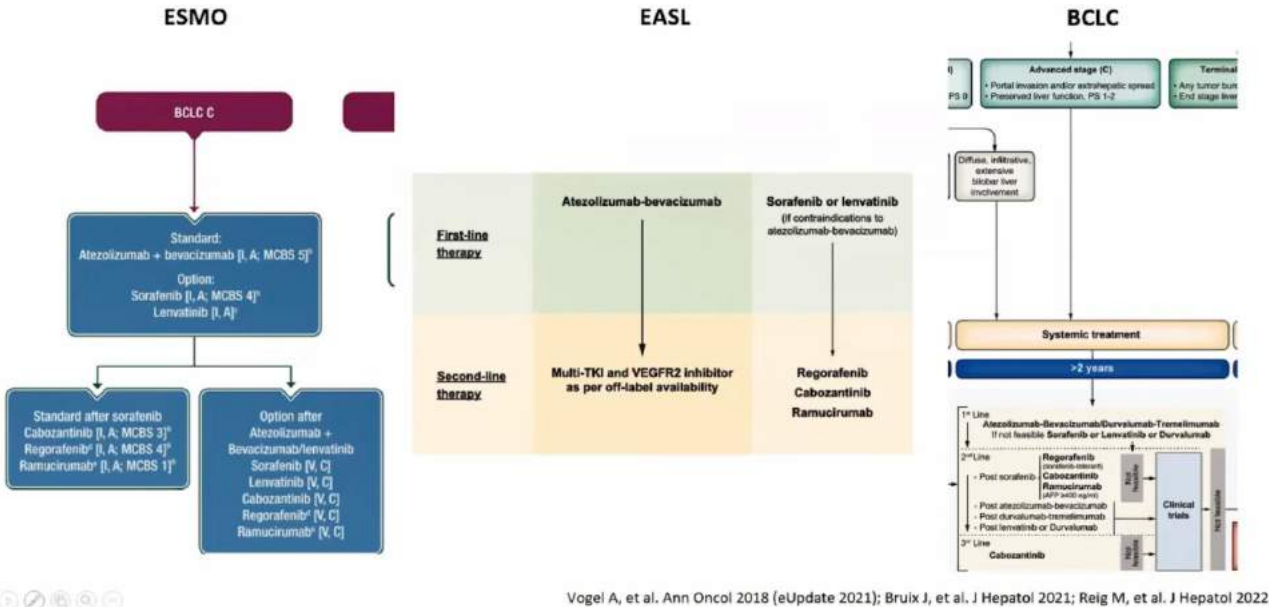
Checkpoint Inhibitors Modulate Plasticity of Innate Lymphoid Cells in Peripheral Blood of Patients With Hepatocellular Carcinoma



Heinrich B, Ruf B, Subramanyam V, et al. Checkpoint Inhibitors Modulate Plasticity of Innate Lymphoid Cells in Peripheral Blood of Patients With Hepatocellular Carcinoma. *Front Immunol*. 2022;13:849958. Published 2022 Jun 27. doi:10.3389/fimmu.2022.849958

Key Takeaway: ICI has an effect on the composition and plasticity of ILCS in peripheral blood. Thus, ILCs from PBMC can be used to study changes in the innate immune system under immunotherapy.

Systemic Therapy for HCC: From Guidelines to the Real World (Western Perspective)



Vogel A, et al. Ann Oncol 2018 (eUpdate 2021); Bruix J, et al. J Hepatol 2021; Reig M, et al. J Hepatol 2022

There is no evidence supporting one regimen over the others, but great differences occur in the reimbursement of cancer drugs with a high impact on the sequence of drugs given.

Key Takeaway: While clinical practice may often differ from the therapeutic guidelines, it is important to analyze the scientific evidence before initiating treatment.

Systemic Therapy for HCC: From Guidelines to the Real World (Asian Perspective)

Real-world practice in HCC among Asian Countries

	Taiwan	Korea	HK	China
1 Line systemic therapy				
Target therapy	*Sorafenib *Lenvatinib (preferred)	Contraindicated for IO *Sorafenib *Lenvatinib	Contraindicated for IO *Sorafenib *Lenvatinib (preferred)	*Sorafenib *Lenvatinib *Donafenib **FOLFOX chemotherapy
• 1L systemic treatments are varied in real world practice in Asian countries under various clinical considerations.				
Immunotherapy or IO combination	*Atezolizumab + Bevacizumab *Lenvatinib + Pembrolizumab (anti-PD-1) *Bevacizumab + anti-PD-1/PD-L1 *Sorafenib + anti-PD-1	*Atezolizumab + Bevacizumab *Durvalumab + Tremelimumab	*Atezolizumab + Bevacizumab *Nivolumab monotherapy or Nivolumab + Ipilimumab	*Atezolizumab + Bevacizumab *Sintilimab + bevacizumab analogue (byvasda) *Camrelizumab + Apatinib *Lenvatinib + Pembrolizumab *SOR/LEN + anti-PD-1

Refs:
Goh, Myung Ji et al. doi:10.3350/cmh.2022.0404
Xie, Diyang et al doi:10.3350/cmh.2022.0402
Su, Tung-Hung et al. doi:10.3350/cmh.2022.0421
Hui, Rex Wan-Hin et al. doi:10.3350/cmh.2022.0399

- Several real-world studies in Asia suggest that 1L ate/beva and lenvatinib are comparable in efficacy.
- Immunotherapy for Child-Pugh Class B HCC patients may not be cost-effective.
- Gut microbiota may serve as a potential biomarker for HCC immunotherapy and needs further exploration.
- Conventional definitions of tumor burden were not optimal for patients with intermediate HCC. The new 7–11 criteria had the best discriminative power in predicting radiologic response and survival in patients with intermediate-stage HCC undergoing TACE.

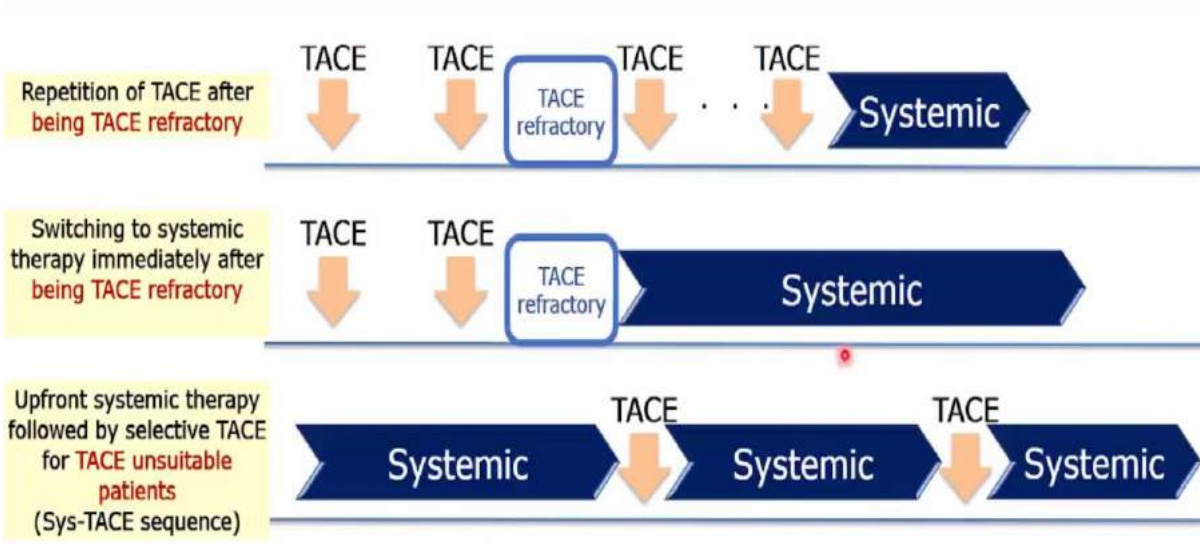
Redefining Tumor Burden in Patients with Intermediate Stage Hepatocellular Carcinoma: the Seven-Eleven Criteria

	Tumor burden		
	Low	Intermediate	High
Up-to-7 criteria	Number of tumors + the largest tumor (cm) ≤7		Number of tumors + the largest tumor (cm) >7
Up-to-11 criteria	Number of tumors + the largest tumor (cm) ≤11		Number of tumors + the largest tumor (cm) >11
5-7 criteria	2 or 3 lesions (any size) 4-7 lesion <5 cm		4-7 lesions ≥5 cm >7 lesions (any size)
Seven lesions criteria	≤7 lesions (any size)		>7 lesions (any size)
7-11 criteria	Number of tumors + the largest tumor (cm) ≤7	7< Number of tumors + the largest tumor (cm)≤11	Number of tumors + the largest tumor (cm) >11

Huang YW, Lee IC*, Huang YH*. Liver Cancer 2021 Nov;10:629–640

Key takeaway: In Asia, the choice of drug regimen differs based on clinical indication, safety and side effects, reimbursement or payment options and availability.

Changes in Treatment Strategy for Intermediate-Stage HCC

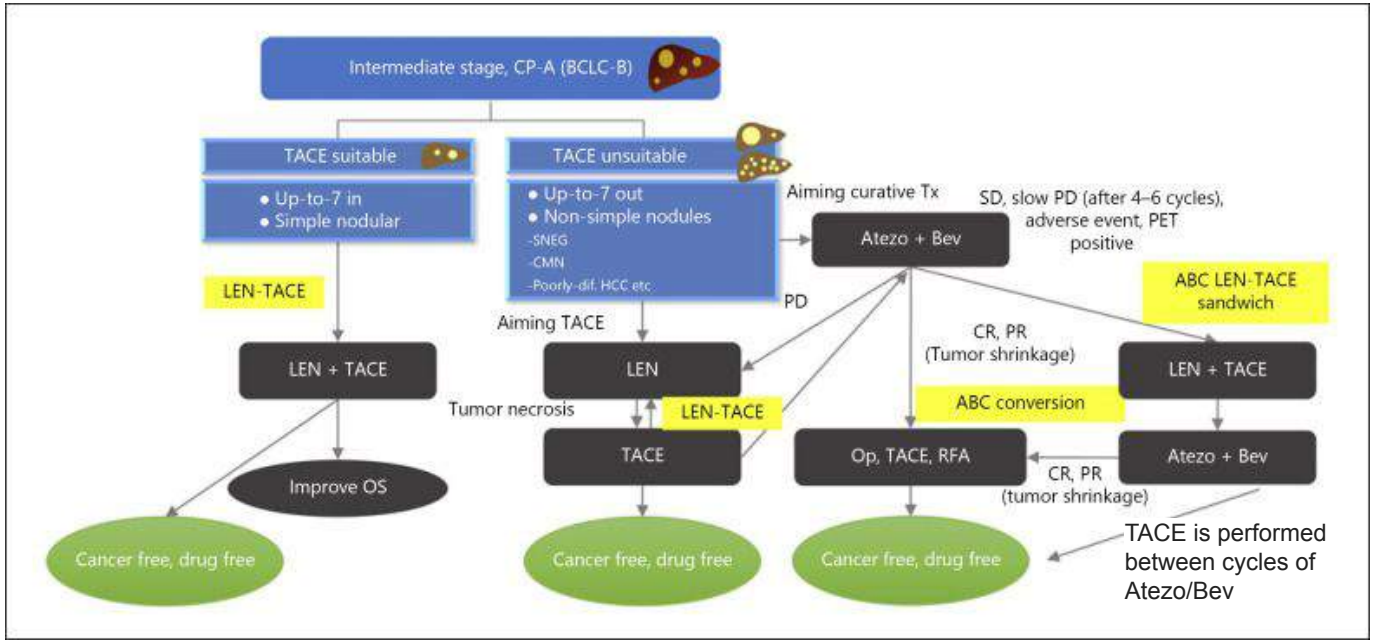


- Not all patients with intermediate stage HCC can be considered for TACE.
- The best candidates for TACE are asymptomatic patients with a solitary or limited multifocal HCC
- AASLD 2020 guidelines recommend upfront systemic therapy followed by locoregional treatment in patients unsuitable for TACE

Key Takeaway: There was an unmet need for intermediate stage HCC patients with high tumor burden

- Kudo M: A Novel Treatment Strategy for Patients with Intermediate-Stage HCC Who Are Not Suitable for TACE: Upfront Systemic Therapy Followed by Curative Conversion. Liver Cancer 2021;10:539-544. doi: 10.1159/000519749
- Kudo, Masatoshi. "Atezolizumab plus Bevacizumab Followed by Curative Conversion (ABC Conversion) in Patients with Unresectable, TACE-Unsuitable Intermediate-Stage Hepatocellular Carcinoma." *Liver cancer* vol. 11,5 399-406. 27 Jul. 2022, doi:10.1159/000526163

Novel Treatment Strategy in Intermediate-Stage HCC



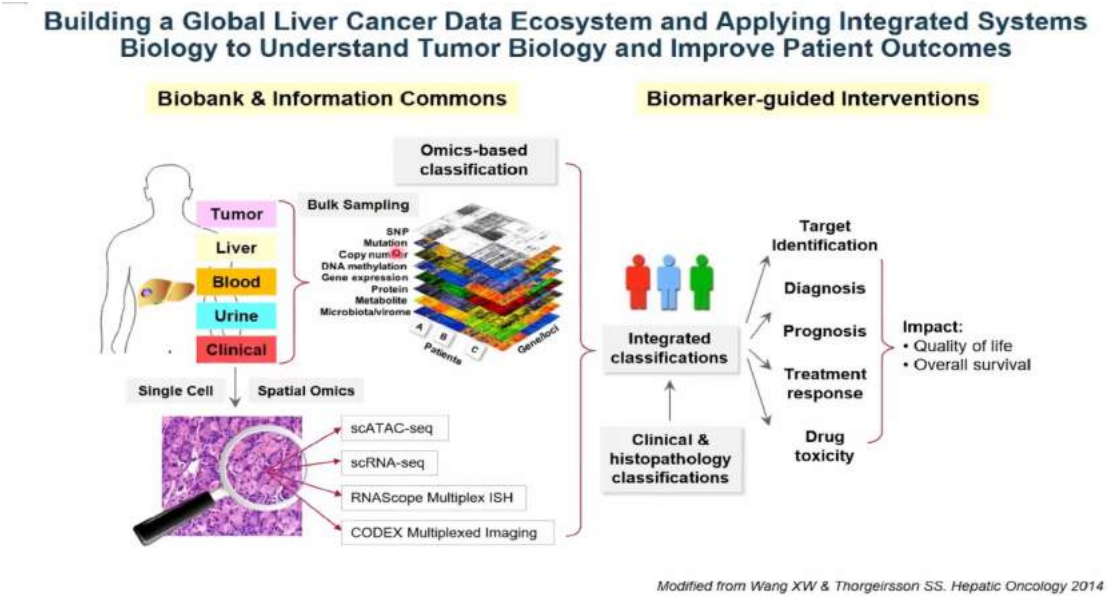
Lenvatinib -TACE sequential therapy significantly improved OS (HR, 0.48; 95% CI, 0.16–0.79; $p < 0.01$). PFS, ORR per mRECIST, and preservation of liver function

Atezo/Bev combination therapy was approved in 2020 following the positive results of the Phase 3 IMbrave150 trial, with ORR of 44% by RECIST 1.1

Key takeaway: ABC-LEN-TACE sandwich therapy may be a breakthrough treatment in patients with PET-positive HCC.

Recent Advances - Early Detection and Immunotherapy in HCC

- There has been increasing interest in the use of immune checkpoint inhibitors for other solid tumors such as HCC
- There is a need to determine why immunotherapy is effective in certain patients but not in others and use this information to develop novel therapies.
- Mass spectrometry for single-cell analysis and Single-cell RNA sequencing (scRNA-seq) have provided a deeper look into immune cell complexity.



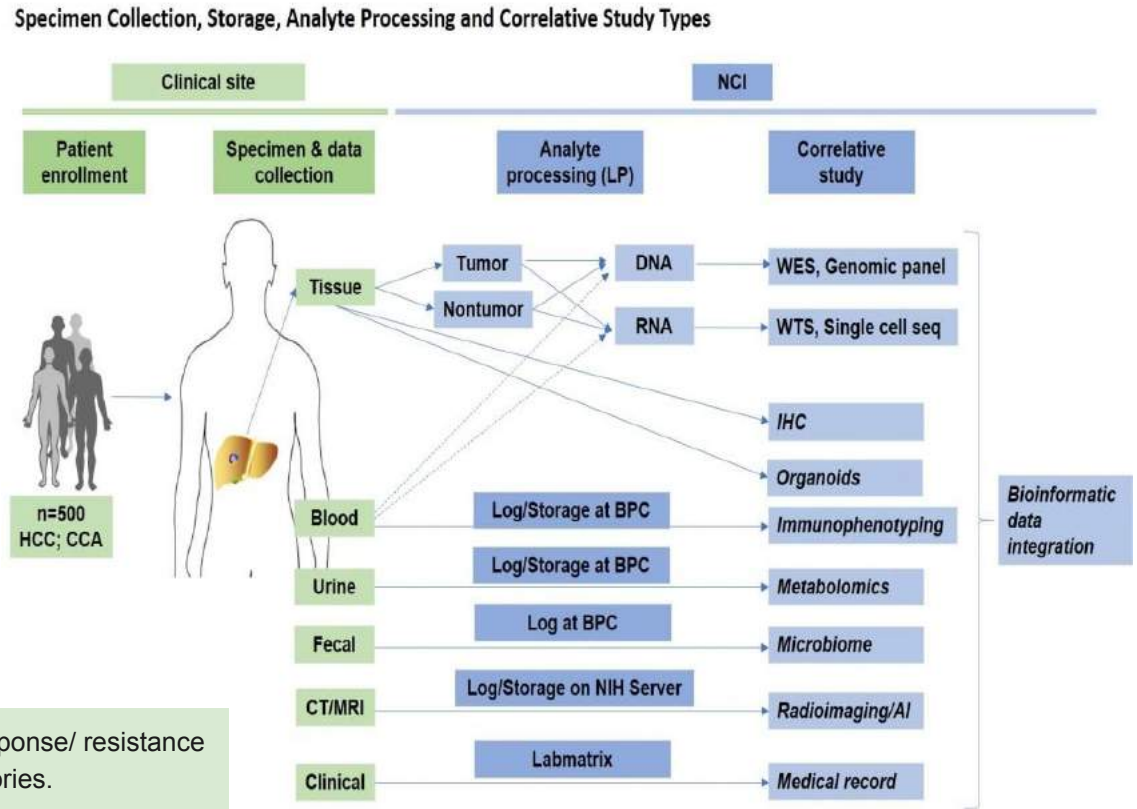
Key takeaway: A differentiated look into the immune composition within the tumour to dissect the exact molecular mechanisms of action is needed to overcome immune treatment failure.

A.Studies of the Evolution of Cell Composition During HCC Progression and Treatment

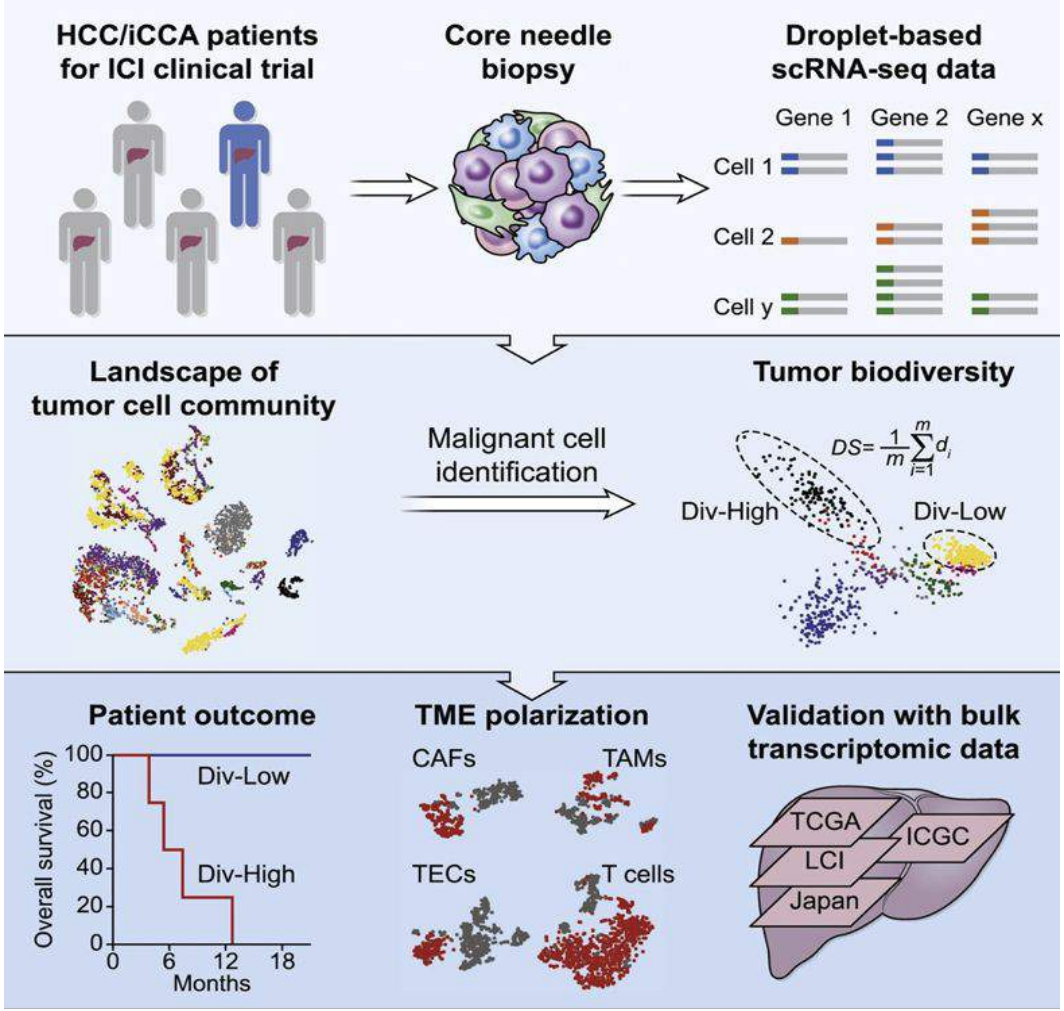
1. **NCI CLARITY Study**

- A biorepository of multiple human biospecimens (tissue biopsy, blood, urine and stool) longitudinally collected (baseline, on treatment, post treatment and follow-up) for multiple downstream correlative studies including large-scale genomics.
- Used to identify patient subgroups, biomarkers and/or molecular signatures associated with immunotherapy response.

https://ccr.cancer.gov/liver-cancer-program/nci-clarity-study



Key takeaway: Researchers can develop predictors for response/ resistance or acquired resistance to immunotherapy, using biorepositories.



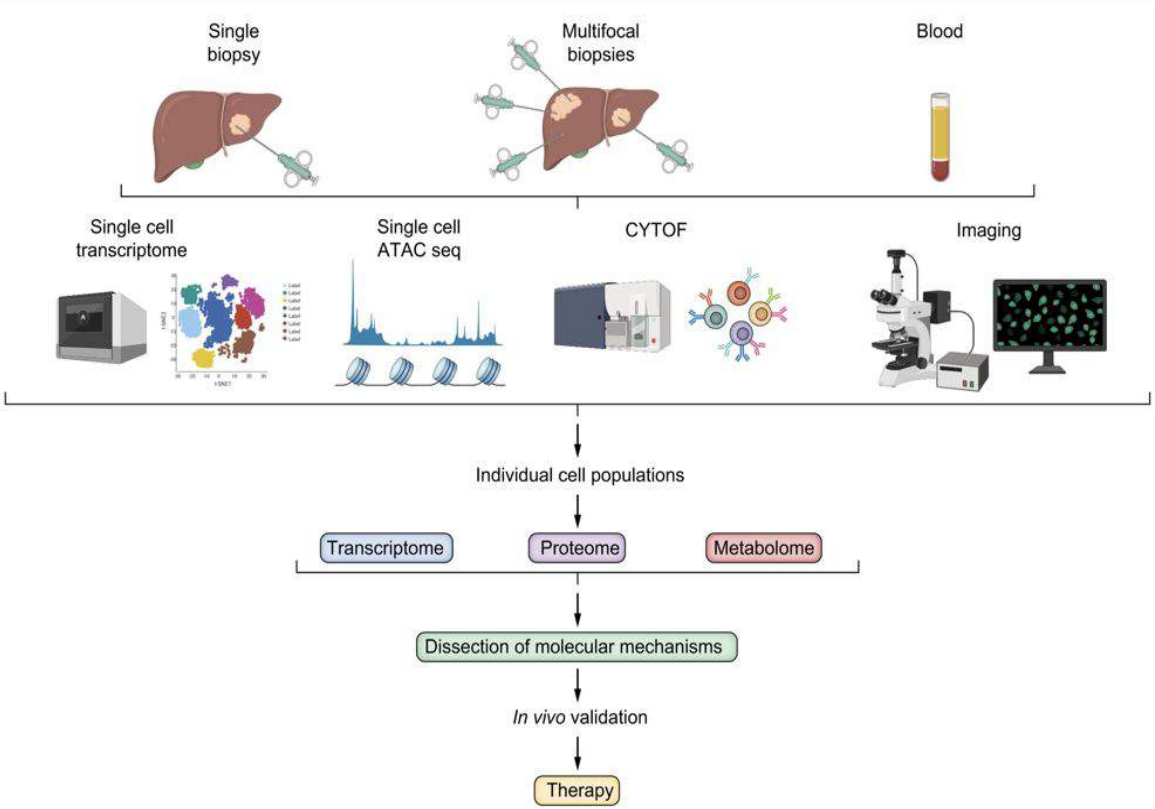
2. Tumor Cell Biodiversity Drives Microenvironmental Reprogramming in Liver Cancer

- There are varying degrees of heterogeneity in malignant cells within and between tumors and diverse landscapes of the tumor microenvironment (TME).
- HCC and ICC have varying degrees of transcriptomic diversity.
- Those with higher transcriptomic diversity were associated with the patient's worse overall survival.
- Tumor-derived VEGF drives microenvironmental reprogramming
- T cells derived from higher heterogeneous tumors showed lower cytolytic activities.

Key takeaway: A transcriptomic diversity score can
- Predict + improve immunotherapy response
- provide a rationale for combining immune checkpoint blockade + anti-vascular treatment

Ma L, Hernandez MO, Zhao Y, et al. Tumor Cell Biodiversity Drives Microenvironmental Reprogramming in Liver Cancer. *Cancer Cell*. 2019;36(4):418-430.e6. doi:10.1016/j.ccell.2019.08.007

B. The Evolution of Hepatocellular Carcinoma at a Single Cell Level



Understanding tumour cell heterogeneity and its implication for immunotherapy in liver cancer using single-cell analysis.

- Intratumoural heterogeneity is a hallmark of liver cancer and single-cell analysis enables analysis of each subpopulation and their interactions.
- ScATAC-seq may provide insights into transcriptional regulations that are associated with immunotherapy.

The single-cell analysis and transcriptomic profiling allows

- Deconvolution of tissue hierarchies
- Identification of rare cell populations.
- Identification of specific molecular alterations responsible for tumorigenesis and progression
- identification of immune subgroups
- identification of processes like clonality and trajectory within T cells identification of different states of activation and exhaustion.

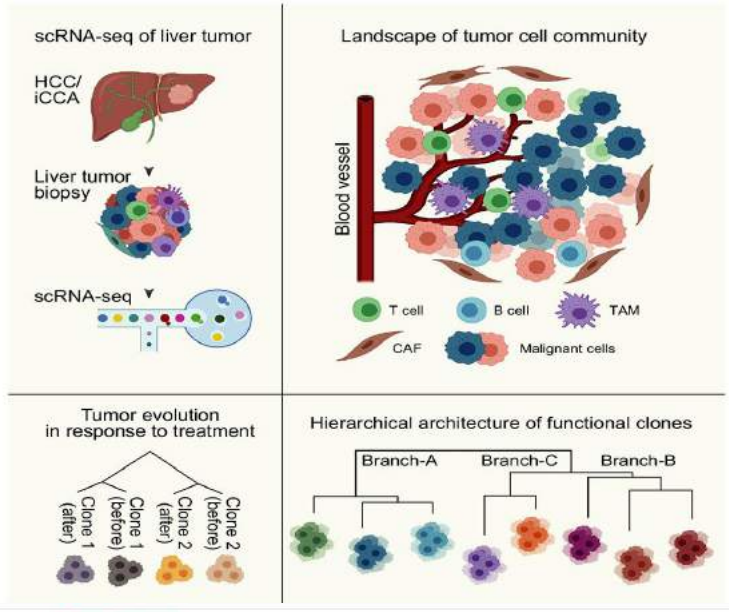
Comparison of tumour infiltrating immune cells with cells from non-tumorous sites can identify organ specific immune cell characteristics and gains information about tumour specific influences on its environment.

Key takeaway: Single-cell analysis enables dissection of molecular mechanisms through transcriptomic, proteomic and metabolomic data on a single-cell level, leading to new personalised therapeutic approaches.

Single-cell atlas of tumor cell evolution in response to therapy in HCC and ICC

- Intratumor molecular heterogeneity is a key feature of tumorigenesis that is linked to treatment failure and patient prognosis.
- Researchers presented a single-cell atlas of liver tumors from patients treated with immunotherapy and described intratumoral cell states and their hierarchical relationship.
- They suggested osteopontin, encoded by the gene SPP1, as a candidate regulator of tumor evolution in response to treatment.

Ma L, Wang L, Khatib SA, et al. Single-cell atlas of tumor cell evolution in response to therapy in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Hepatol*. 2021;75(6):1397-1408. doi:10.1016/j.jhep.2021.06.028



Single-cell Atlas in Liver Cancer (scAtlasLC)

scAtlasLC (single-cell Atlas in Liver Cancer) is a publicly available data portal of single-cell transcriptomic profiles of tumor cell communities in HCC and ICC.

It can be used to

- evaluate gene expression in malignant cells and various non-malignant cells in liver cancer
- determine gene expression in different subtypes of stromal cells and immune cells.

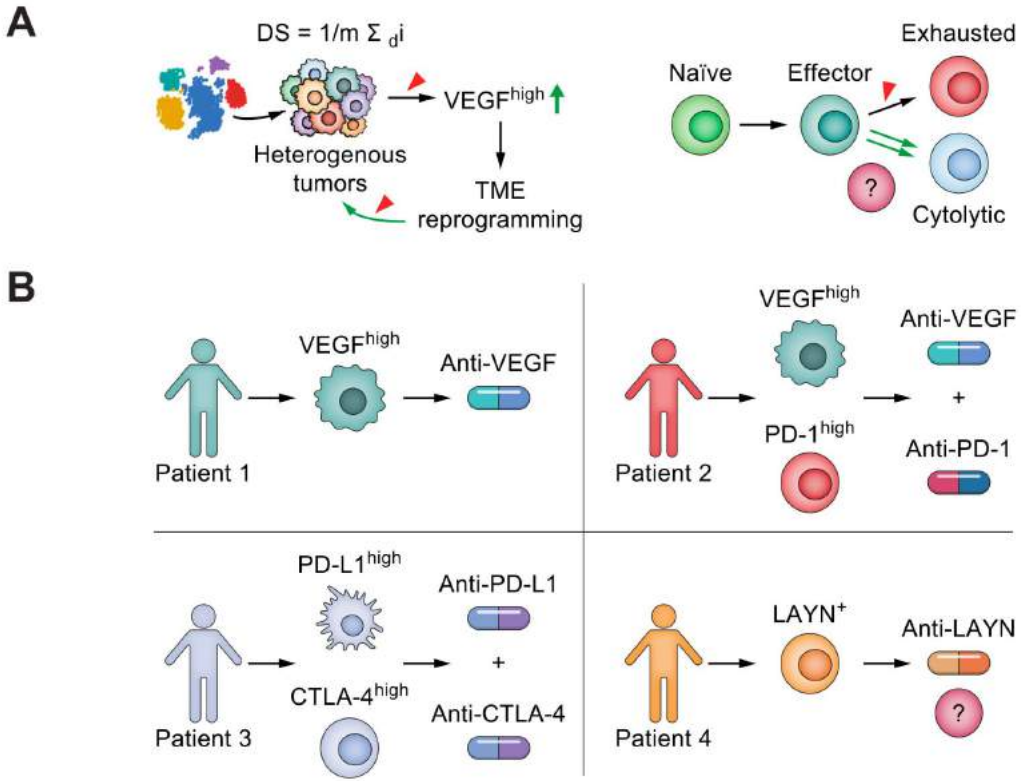
https://scatlaslc.ccr.cancer.gov/#/

Application of single cell analysis in future treatment regimens

Key takeaway:

(A) molecular interactions and cell development into a tumour supportive state could be interrupted on different levels.

(B) personalised treatment approaches based on cellular compositions and subgroups can be developed for every single patient.



Heinrich, Sophia, et al. "Understanding Tumour Cell Heterogeneity and Its Implication for Immunotherapy in Liver Cancer Using Single-Cell Analysis." *Journal of Hepatology*, vol. 74, no. 3, 2021, pp. 700-715, https://doi.org/10.1016/j.jhep.2020.11.036

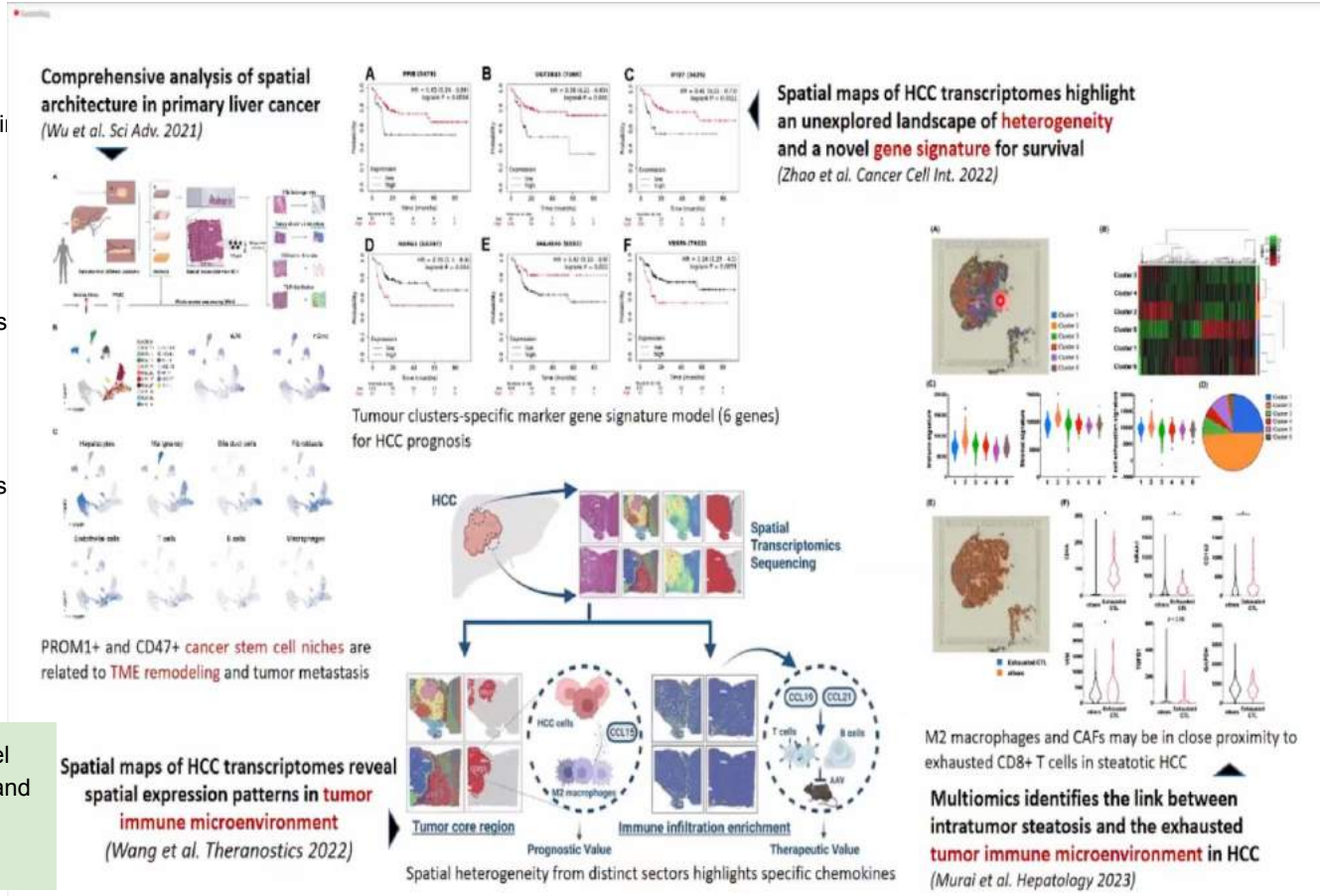
Spatial Transcriptomics : Latest Technology in Molecular Analysis of HCC

Spatial transcriptomics - molecular profiling method that allows scientists to measure all the gene activity i a tissue sample and map where the activity is occurring. It facilitates a refined analysis of spatial arrangement of cells and their interactions.

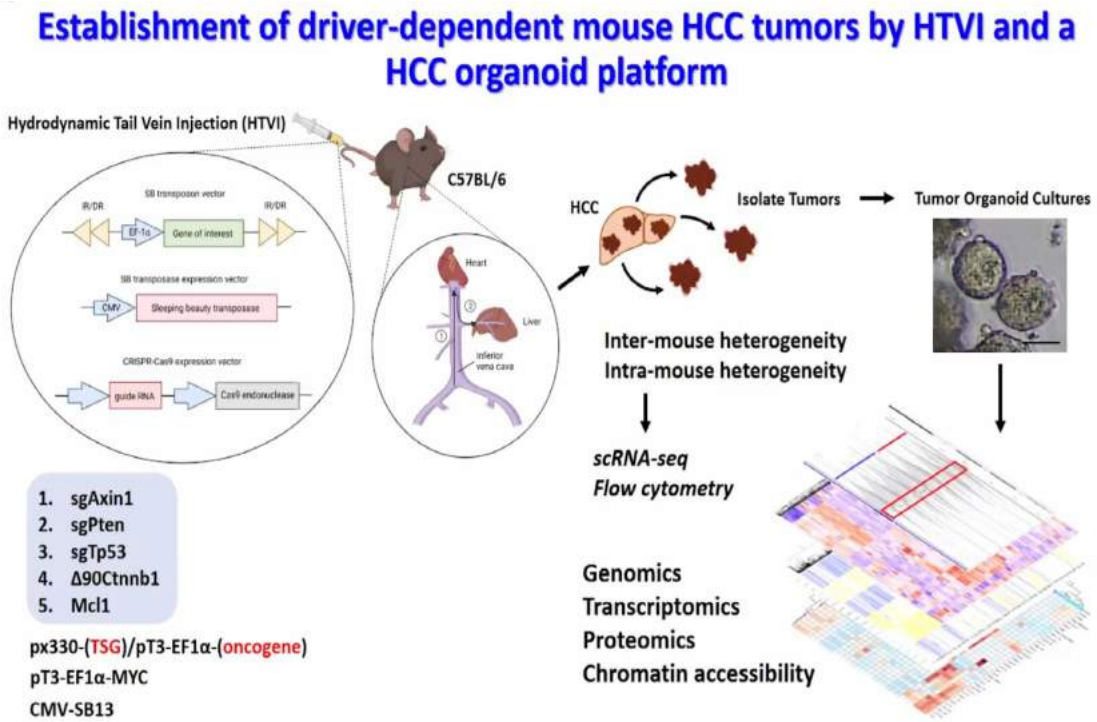
Advantages:

- The endogenous spatial organization of cells and their whole transcriptome profiles are preserved.
- Coupling of histological, molecular, and cellular information
- Applicable to both frozen and FFPE samples
- Lesser tissue inputs required

Key takeaway: Spatial transcriptomics provides novel insights into the complex ecosystem of liver cancer and have the potential to improve individualized cancer prevention and drug discovery.



C. Genetically Defined, Syngeneic Organoid Platform for Understanding Heterogeneity and Response to Therapy in Liver Cancer



- HCC patients present high inter tumor heterogeneity, yet conventional HCC mouse models fail to capture this high diversity limiting mechanistic and translational studies
- Researchers have established and characterized distinct driver gene combinations at various OMIC levels.
- This induced murine HCC models and their corresponding organoids.
- The models recapitulate the human HCC transcriptional subclass.
- Preliminary data demonstrates the utilization of

Key takeaway: An easily scalable murine HCC organic platform can be used to assess drug response heterogeneity with validation in human HCC patient-derived organoids.

Combined Hepatocellular-Cholangiocarcinoma

(cHCC/CCA)

Diagnosis and Management

This section contains the synopsis of the following sessions:

Session: APASL Symposium 15- HCC/CC: Epidemiology, Natural History, Diagnosis, and Staging

Moderators: Po Chin Liang (Taipei) / Shiu-Feng Huang (Miaoli)

Speakers and Topics:

1. Yasuni Nakanuma (Kanazawa) Pathological Diagnosis of Combined Hepatocellular-cholangiocarcinoma (cHCC/CCA)

2. Li-Tzong Chen (Kaohsiung) Precision Medicine in Combined Hepatocellular and Cholangiocarcinoma

3. Po-Da Chen (Taipei) Long-Term Survival of Combined Hepatocellular Carcinoma-Cholangiocarcinoma:

1 symposium = 3 lectures/talks covered in 5 slides

Pathological Diagnosis of Combined Hepatocellular-cholangiocarcinoma (cHCC/CCA)

- Rare primary liver malignancy - 2-5% of primary liver carcinomas
  Exhibits hepatocytic and biliary differentiation within the same tumor.

- Neoplastic transformation of a stem cell subpopulation may explain hepatocarcinogenesis.

WHO 2000 DEFINITION	WHO 2010 DEFINITION	WHO 2019 DEFINITION
cHCC - CCA was defined as primary liver carcinoma with both hepatocytic and cholangiocytic differentiation within the same tumor.	cHCC - CCA Was subdivided into - Classical cHCC - CCA and Stem cell cHCC - CCA variants	cHCC - CCA is diagnosed by the unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor - regardless of the percentage of each component. The diagnosis is based primarily on H&E morphology with support from IHC markers.

Key Takeaway: Recent studies have shown the pathological correlation between stem cells and cHCC - CCA. They have morphology + immunophenotypic expression + clinicopathological features of biliary, hepatocytic, and stem/progenitor cells

Subtypes of the stem cell variant include:

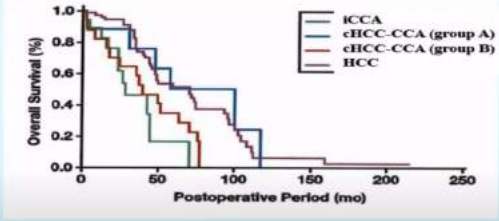
A. Typical
B. Intermediate
C. Cholangiocellular

They are differentiated using IHC for biliary and hepatocytic markers

Immunohistochemical markers for identifying hepatocytic, cholangiocytic differentiation, and stem/progenitor cells

	Hepatocytic differentiation	Biliary differentiation	Stem cell differentiation with stem cell morphology
Common markers	Arginase-1	CK7	CK19
	HepPar-l	CK19	NCAM (CD56)
	CD10	pCEA	EMA (MUC1)
	pCEA	mCEA	c-kit (CD117)
	AFP	EMA (MUC1)	CD133

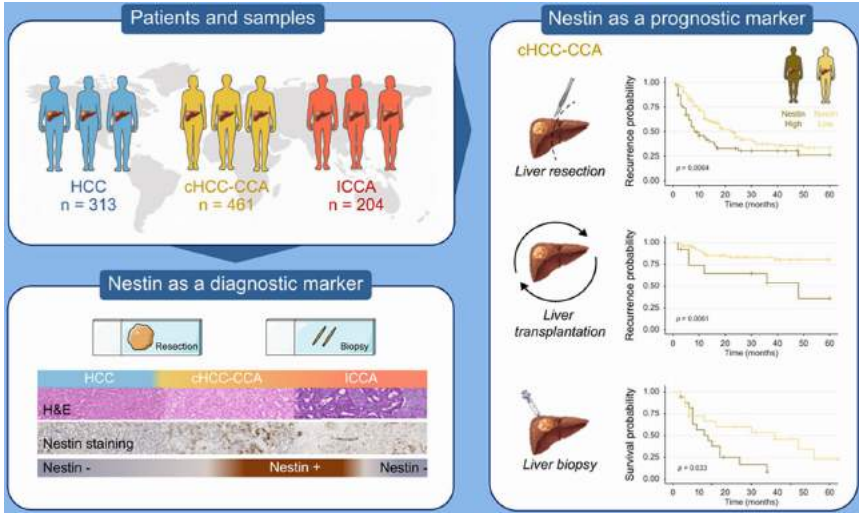
Postoperative overall survival of iCCA, cHCC-CCA and HCC



cHCC-CCA (group A): containing less than 5% of either of subtypes
cHCC-CCA (group B): containing more than 5% of either of subtypes

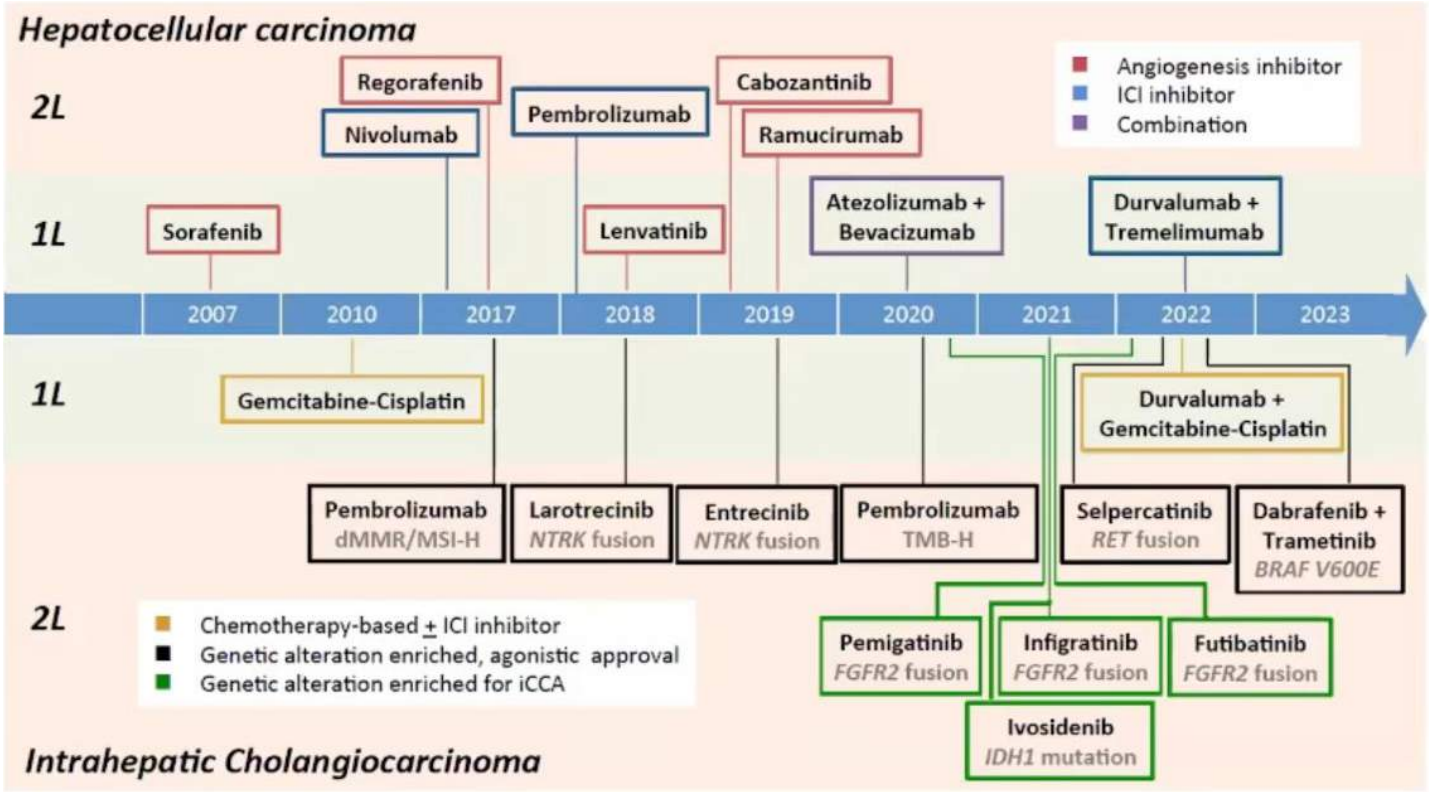
New cell marker used to diagnose cHCC - CCA

- Nestin : embryonic type VI intermediate filament identified as a neural stem cell marker
- cHCC - CCA show significantly high expressions of nestin, which is used to differentiate between cHCC - CCA and HCC
- Prognostic value- Nestin + tumors had worse outcomes after surgery and transplants



Key Takeaway: Nestin IHC may be used to refine risk stratification and improve treatment allocation for patients

Precision Medicine in Combined Hepatocellular and Cholangiocarcinoma



Key takeaway: Immune mediated therapy for ICC have many more tumor agnostic drugs approved for use in the last few years, compared to treatments for HCC

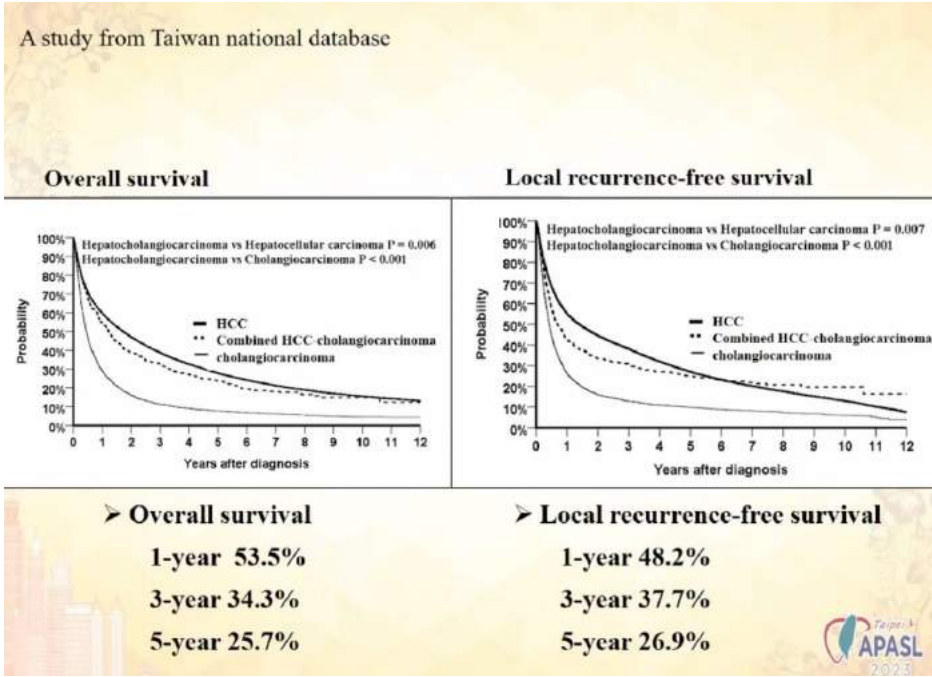
Long-Term Survival of c-HCC- CC- A Nationwide Study in Taiwan

Objective: showcase the clinical features and long-term prognosis of cHCC-CC

Methods: 100,754 patients with newly diagnosed liver cancer between 2004 and 2013 from the Taiwan Cancer Registry.
Primary outcome measures: overall survival and local recurrence-free survival
Median follow-up time: 60 months (29-120 months).

Results:

- HCC-CC tended to share some characteristics with HCC, including increased frequency of stage I cases, high individual tumor rates, and similar patterns of viral hepatitis B and hepatitis C infections.
- In contrast, HCC-CC showed malignant behavior similar to that of CC, as high-grade tumor cell differentiation and presentation of jaundice were predominant in HCC-CC and CC compared to HCC.



Chen, Po-Da & Chen, Li-Ju & Chang, Yao-Jen & Chang, Yun-Jau. (2021). Long-Term Survival of Combined Hepatocellular-Cholangiocarcinoma : A Nationwide Study. The oncologist. 26. 10.1002/onco.13893.

Out of 530 patients with cHCC-CC:

- The mortality rate was 79.2%
- The local recurrence rate was 65.3%
- 46% had a primary tumor of less than 5 cm
- 51.3% had a single tumor
- 44.5% underwent surgery as the initial treatment
- 76% had peri-operative AFP levels less than 400 ng/ml
- 60.8% had cirrhosis of the liver
- 47.2% had a history of HBV infections
- 14.7% had a history of HCV infections
- 11.3% had a history of HBV +HCV infections
- The most prevalent stage in cHCC-CC and HCC was stage 1, in contrast to CC where stage 4 was the most prevalent stage.
- Patients were predominantly male in cHCC-CC and HCC but not in CC.

Key Takeaways

- Although cHCC-CC reflects the malignant behavior of CC, it should be characterized as a subtype of HCC, as it tends to share more characteristics with HCC than with CC
- With careful selection of patients, curative resection and TACE might benefit the survival of patients with HCC-CC.
- Although short-term overall survival is inferior to HCC, its long-term overall survival is similar to HCC.

Cholangiocarcinoma

This section contains the synopsis of the following session:

Session: APASL Symposium 15- HCC/CC: Epidemiology, Natural History, Diagnosis, and Staging

Lecture- Chih-Horng Wu (Taipei) Imaging Subclassification of Intrahepatic Cholangiocarcinoma: A Correlation With Pathological Findings and Prognoses

1 lecture/talk covered in 2 slides

Cholangiocarcinoma (CC)

- 2nd most common primary malignant hepatic tumor after HCC
- Microscopically similar to adenocarcinoma

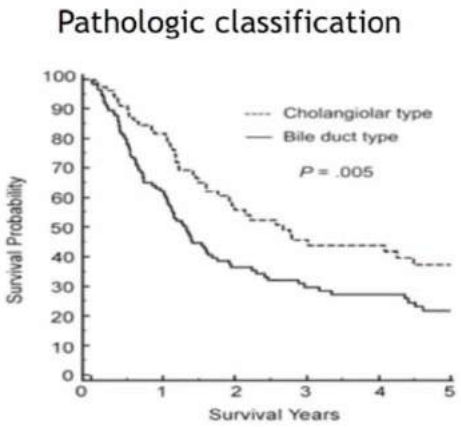
Types:

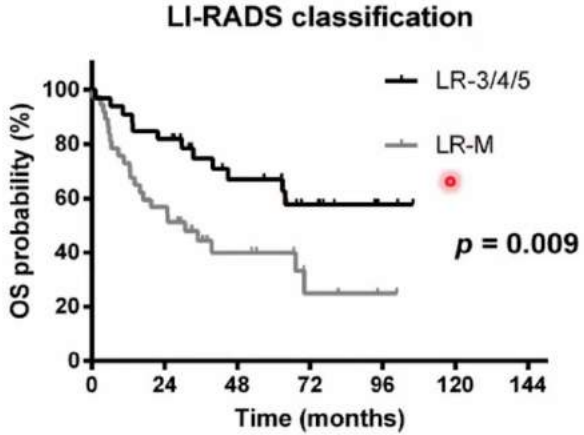
- Extrahepatic CC
- Hilar CC
- Intrahepatic (ICC) - 10% predominance

ICC is further divided into two types, differentiated by IHC

- Bile duct type - S100P, TTF1 AND AGR2 +
- Cholangiolar type - N-Cadherin +

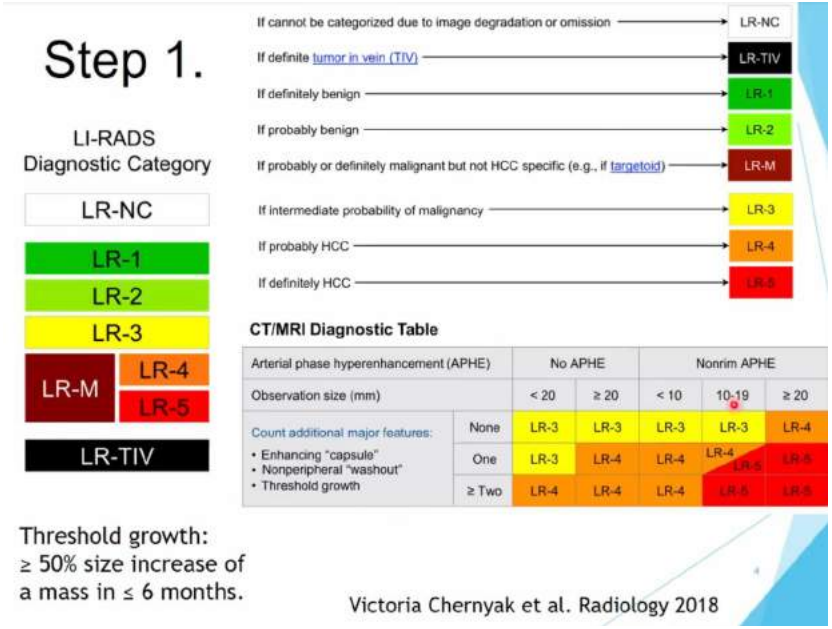
Similar survival curve between Pathologic and LI-RADS classification

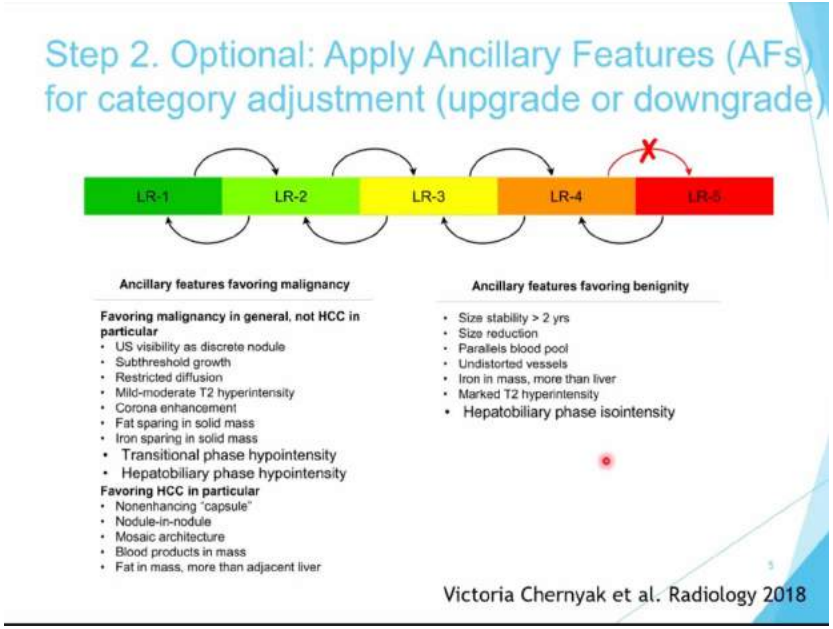




Imaging Subclassification of Intrahepatic Cholangiocarcinoma: A Correlation With Pathological Findings and Prognoses

Since 2018 the American Association for the Study of Liver diseases (AASLD) has used LI-RADS for diagnosis and staging of HCCs
LI RADs system uses CT MRI with extracellular agents (ECA) or MRI with hepatobiliary agents (HBA) for high-risk patients with cirrhosis, liver transmit candidates with HCC and other liver diseases





Key takeaway: Studies show that both IHC (pathological) and LI RADS-based classification show similar survival curve. So LI-RADS can be used to predict survival in ICC and HCC and serves as a good lexicon between physicians and radiologists

MAFLD

Diagnosis, Natural history, Biomarkers and Cancer

This section contains the synopsis of the following sessions:

APASL Symposium 6-MAFLD: Diagnosis, Natural History, Biomarkers, and Cancer

1. Rohit Loomba San Diego Natural History of MAFLD
2. Grace Lai-Hung Wong Hong Kong Approaches for the Prediction of MAFLD and Fibrosis
3. Shiu-Feng Huang Miaoli HCC and Fatty Liver: A Study in Taiwan
4. Yoshio Sumida Nagakute MAFLD in Japan and the Risk Factor for HCC

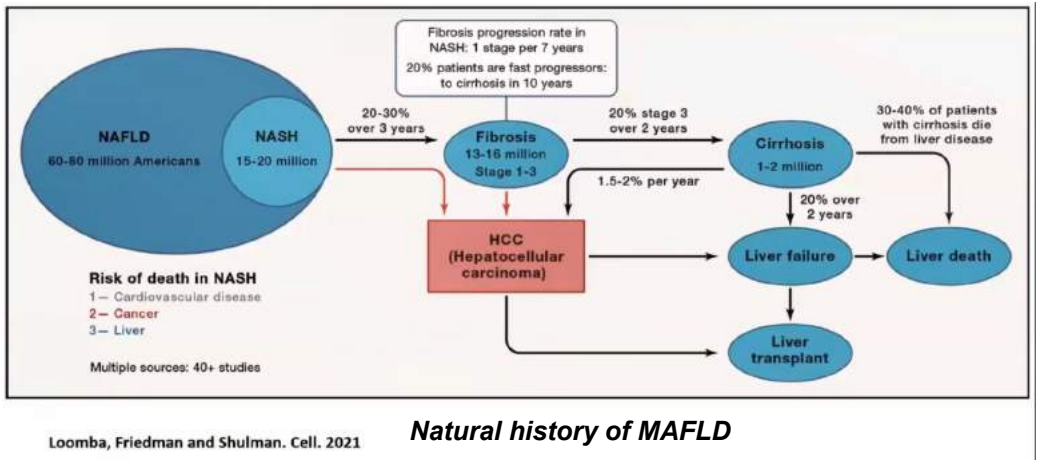
1 symposium = 4 lectures/talks covered in 10 slides

Epidemiology and Natural History

MAFLD is present in 1 in 4 people worldwide
More common in Asian and Indian populations

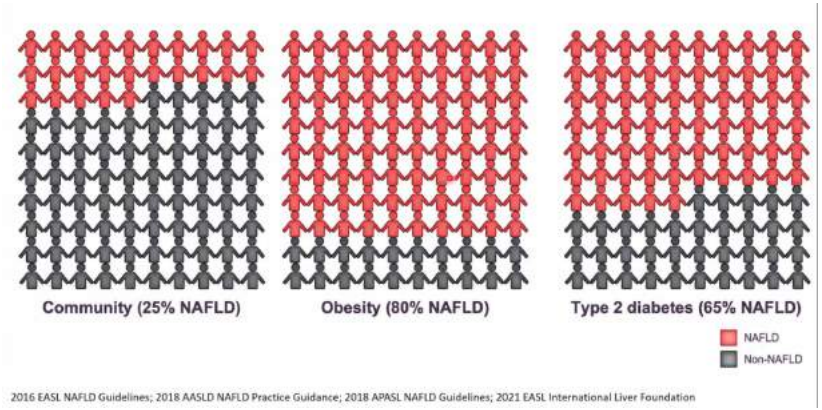
Risk factors include

- Obesity
- Hypertension
- Increased TGL
- Insulin resistance
- Diabetes
- PNPLA3, TM6SF2, MBOAT7, HSD17B13 genotypes



Loomba, Friedman and Shulman. Cell. 2021

Natural history of MAFLD

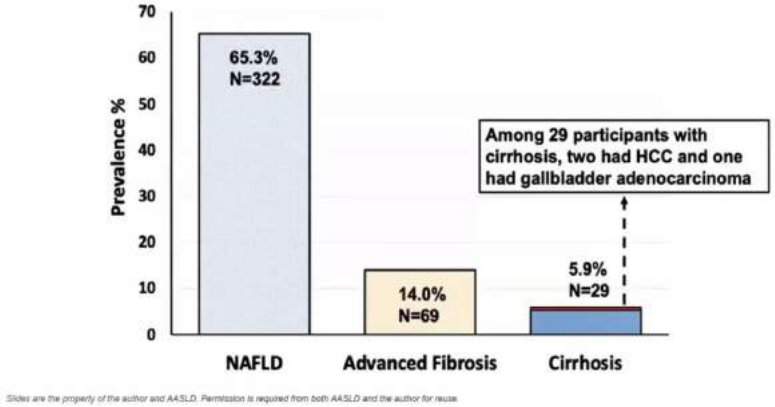


Key Takeaway:

MAFLD is diagnosed either on biopsy or imaging evidence of steatosis (>5% liver fat) in people who consume little or no alcohol without any other cause for liver disease.

Factors determining severity of MAFLD

- Viral hepatitis infections contributed mainly to the disease severity of MAFLD patients
- Lean MAFLD patients carrying metabolic abnormalities had a high risk of advanced fibrosis[1]
- Diabetics have higher risk for advanced fibrosis [2]
- Cardiovascular disease risk increases with worsening disease severity. CVS complications frequently dictate the outcome of NAFLD.[3]
- Fibrosis predicts long term outcomes of NAFLD.[4]
- Increasing fibrosis leads to increased risk of liver related events like: variceal bleeding, ascites, encephalopathy and HCC.[5]

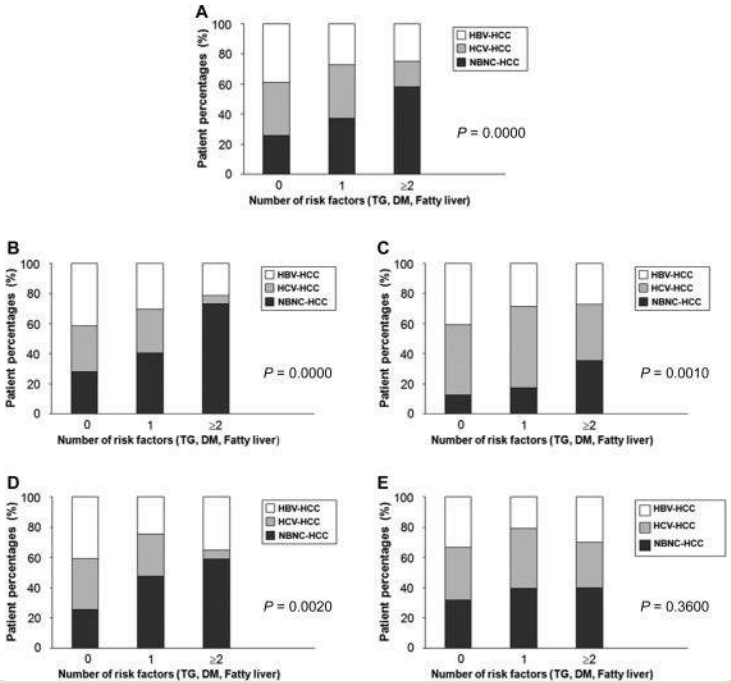


Prevalence of NAFLD, Fibrosis and Cirrhosis in Patients with Diabetes

Key takeaway: The prognosis of MAFLD depends on various factors that affect disease severity and associated morbidity.

1. Huang JF ILC 2022, P3094
2. Docheve I et al Aliment Pharmacol Ther 2016
3. Targer G et al, NEJM 2010
4. Angulo P et al Gastro 2015
5. Sanyal AJ et al NEJM 2021

Metabolic risk factors are associated with NBNC-HCC in Taiwan, an endemic area of chronic hepatitis B



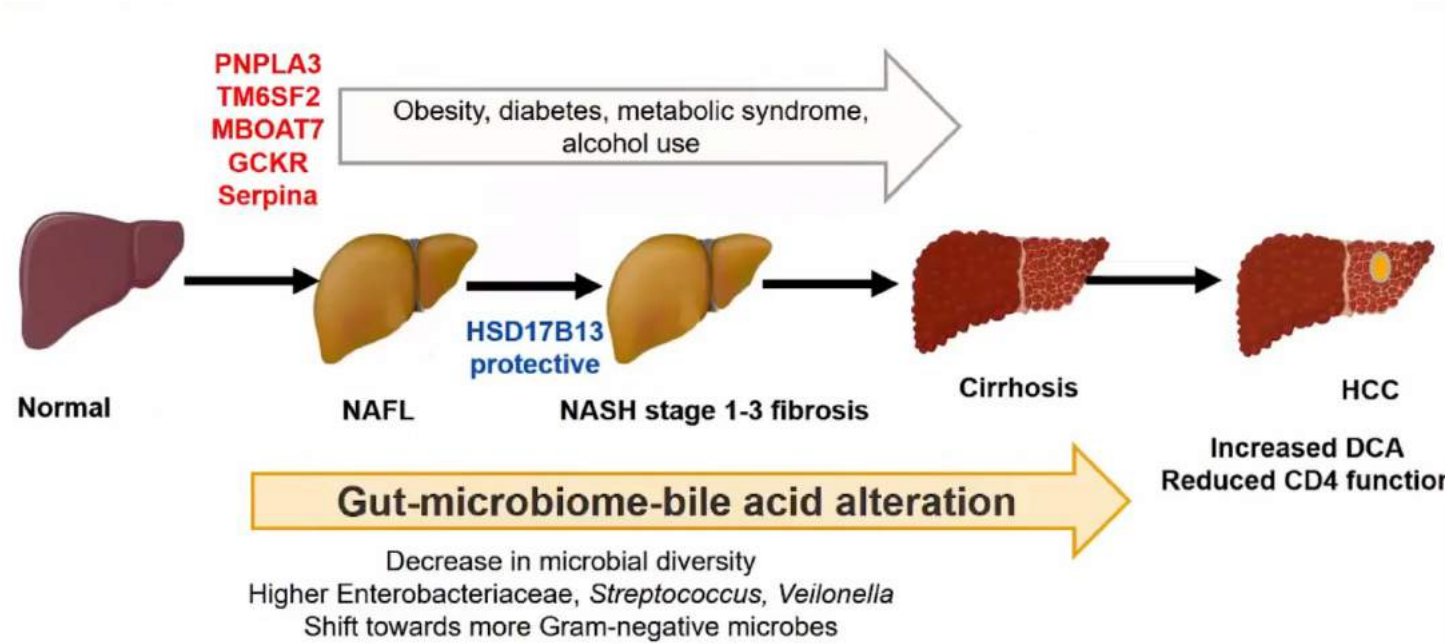
Trend analyses of the difference between sexes for three risk factors, fatty liver by echography, TG level >160 mg/dL, and DM history, in patients with HCC.
(A) Nonalcoholic-noncirrhotic male patients (n = 423).
(B) Nonalcoholic-noncirrhotic female patients (n = 131).
(C) Nonalcoholic-cirrhotic male patients (n = 248).
(D) Nonalcoholic-cirrhotic female patients (n = 107).

Only female patients with HCC and cirrhosis with no alcoholism showed no significant difference when compared with matched patients with HBV-HCC or HCV-HCC.

Key takeaway:
The clinical characteristics of patients with NBNC-HCC differ from those of patients with HBV-HCC or HCV-HCC.
Metabolic risk factors, such as fatty liver (by echography), high TG levels (>160 mg/dL), and DM history, were significantly associated with patients with NBNC-HCC, especially those without alcoholism and cirrhosis.

Huang, Shiu-Feng et al. “Metabolic risk factors are associated with non-hepatitis B non-hepatitis C hepatocellular carcinoma in Taiwan, an endemic area of chronic hepatitis B.” *Hepatology communications* vol. 2,6 747-759. 18 Apr. 2018,

Genetic Environment for the progression of MAFLD



Key takeaway: improved understanding of the genetics involved in MAFLD will help in treatment and risk stratification.

Non invasive parameters for Diagnosis of MAFLD

Test	Advanced cirrhosis and fibrosis	Hepatic Steatosis
Serum	FIB-4 ELF	Fatty liver index Hepatic steatosis index NAFLD Ridge score
Imaging	VCTE (Transient elastography) MRE for LSM (Magnetic resonance elastography) SWE (Shear wave elastography) Acoustic radiation force impulse (ARFI)	Abdominal ultrasound Controlled attenuation parameter MRI-PDFF or proton MR spectroscopy

Scoring for prognosis:

1. HA SCORE : Age, obesity, AST, ALT, Blood sugar, hyaluronic acid
2. ELF score : Age, TIMP 1, amino terminal peptide of procollagen III ,hyaluronic acid
3. BAAT score : Age, BMI, ALT, Triglyceride
4. NAFLD score : Age, hyperglycemia, BMI, platelet, albumin, AST/ALT
5. Fibrometer : Age, body weight, platelets, AST,ALT, ferritin, glucose

At Risk NASH/ NASH with stage 2 fibrosis

- FAST: CAP, VCTE, AST
- MAST: MRI-PDFF,MRE,AST
- MEFIB: MRE 3.3 KPA + FIB 41.6

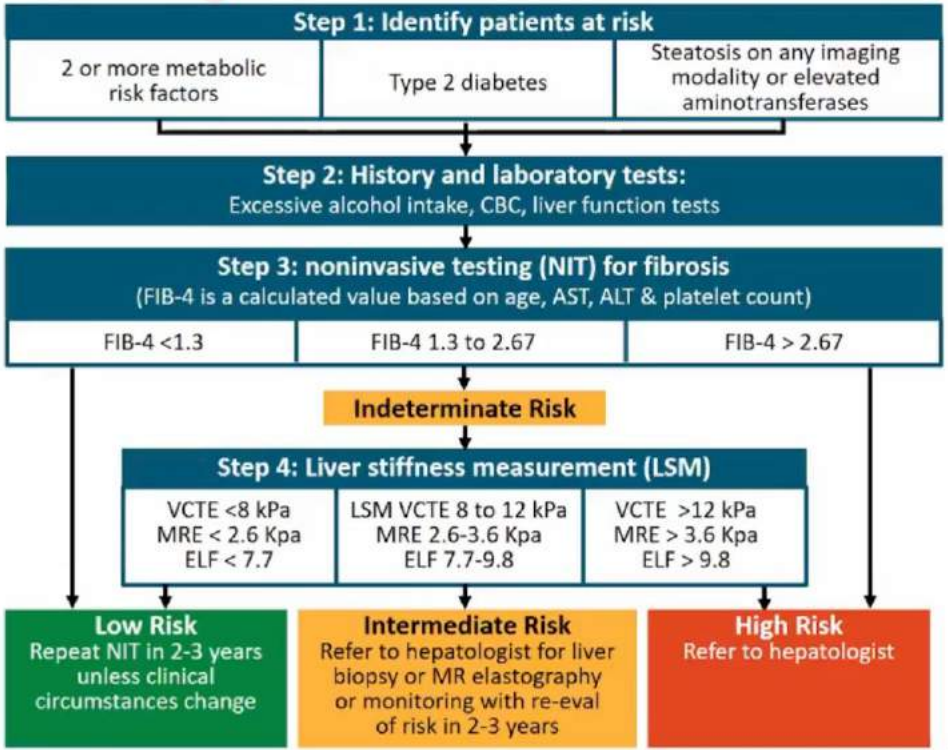
Key takeaway: Need for non-invasive testing:

- For serial monitoring in drug trials
- Objective measurements
- Less influenced by sampling problems
- Less expensive than liver biopsy

Development is difficult as liver biopsy is used as the gold standard for comparison, and a marker of fibrogenesis versus fibrosis.

2021 AGA: Clinical Care Pathway- Screening for Advanced Fibrosis

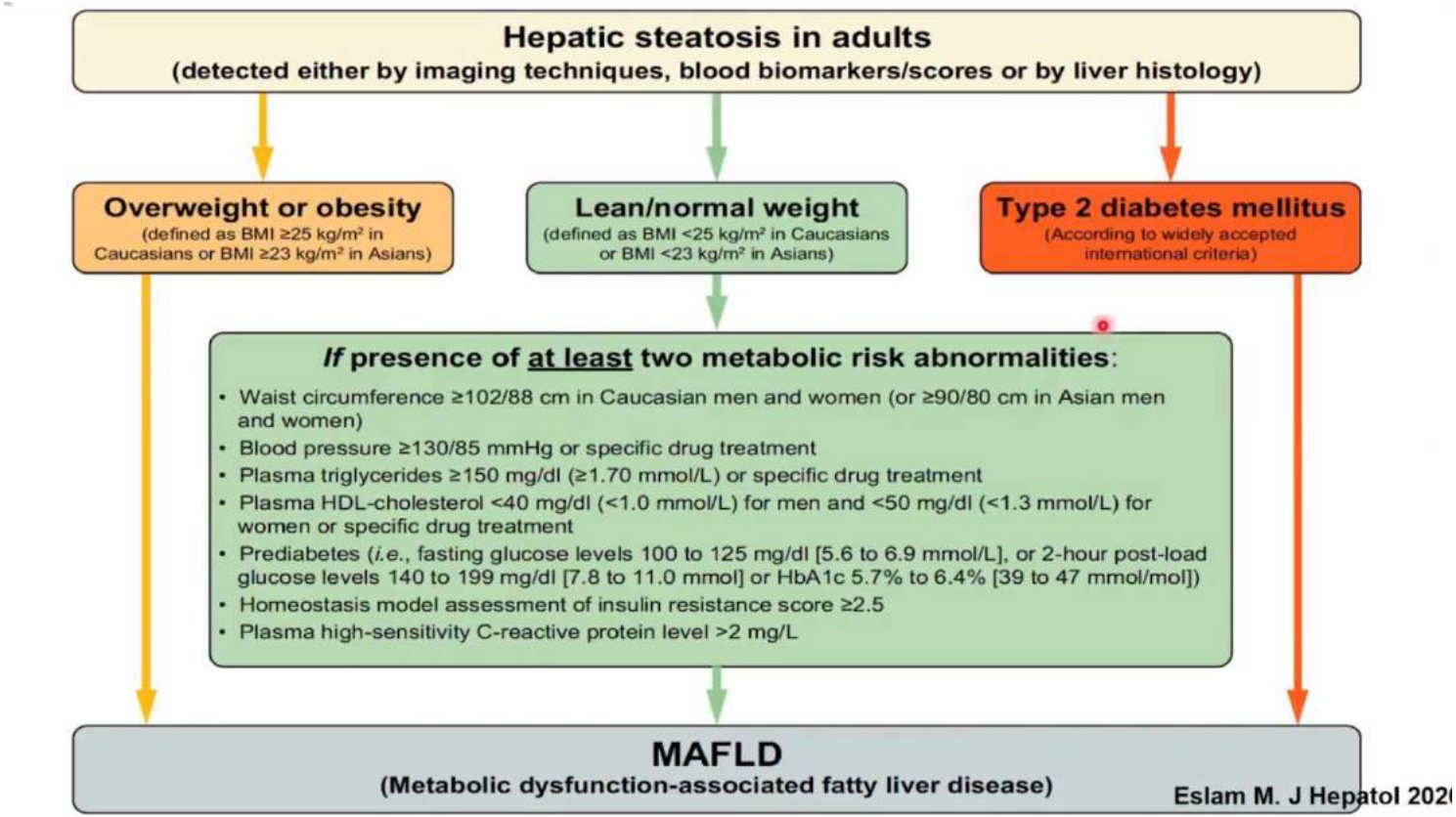
Primary care, endocrinologists, gastroenterologists, and obesity specialists should screen for NAFLD with advanced fibrosis



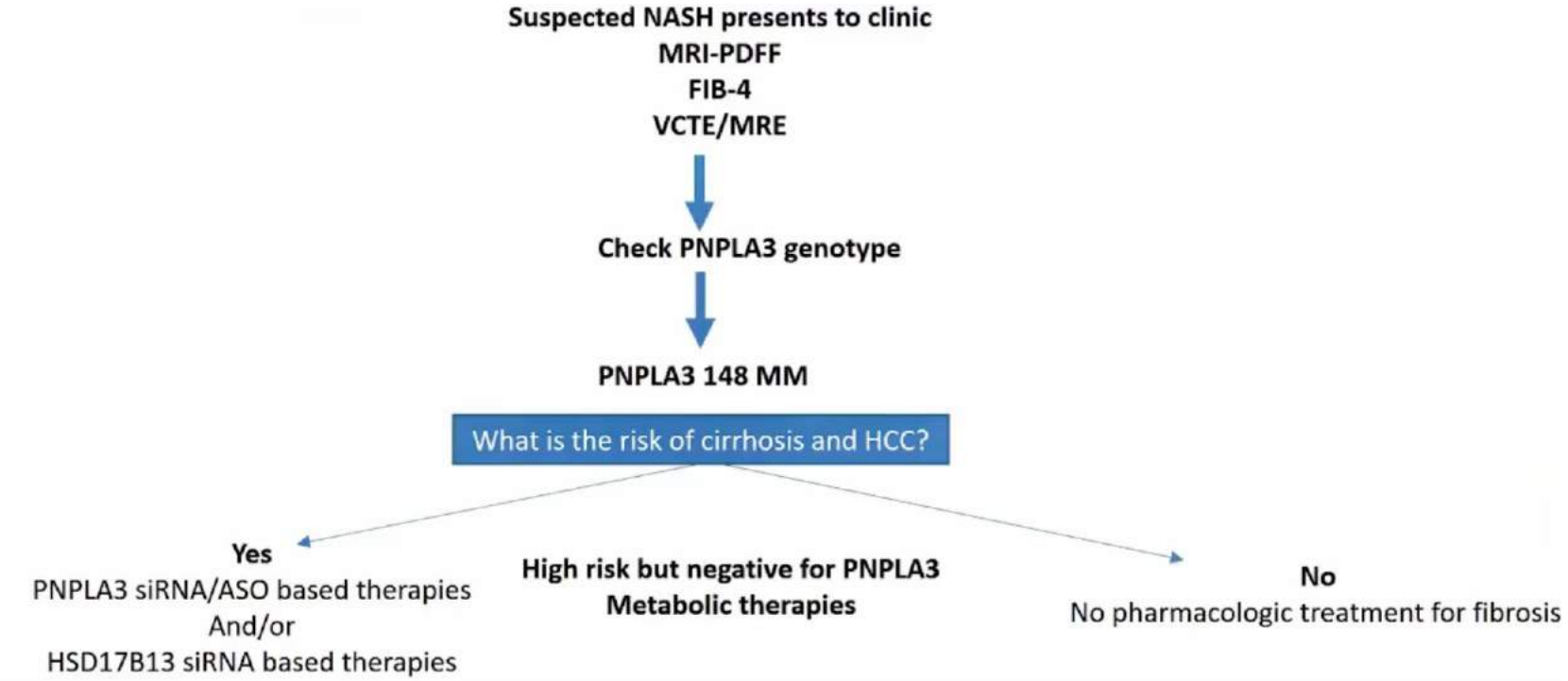
Kanwal. Gastroenterology 2021;161:1657–1669

Slide credit: clinicaloptions.com

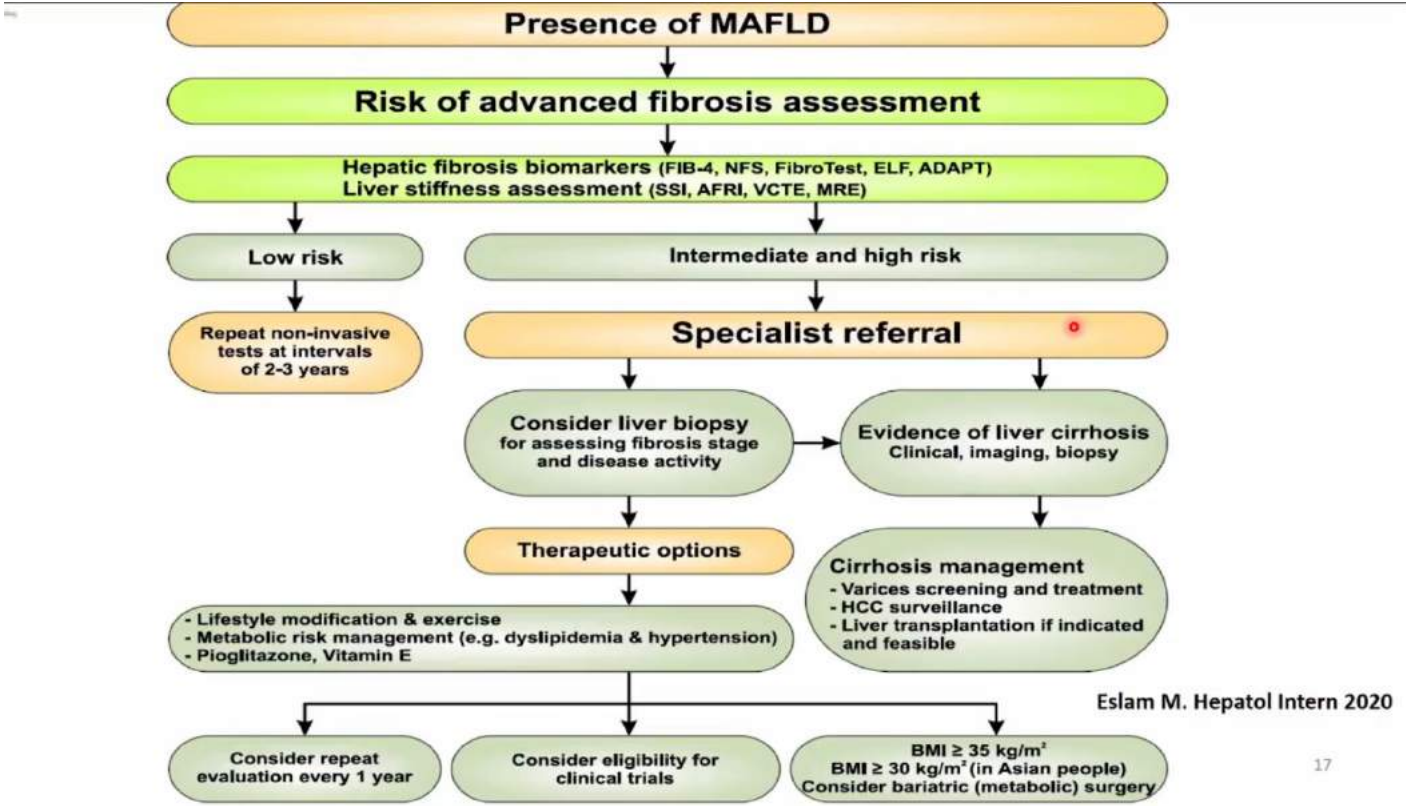
Diagnostic Algorithm for MAFLD



Precision medicine paradigm for NASH treatment



Treatment guidelines for MAFLD



AI based approaches for NAFLD

AI approach	Advantages	Disadvantages
Logistic regression	Easy to implement, interpret Very efficient to train.	Overfitting Constructs linear boundaries
Decision tree	Less effort for data preparation during pre-processing.	Training is relatively expensive as the complexity and time
Random forest	Reduces overfitting problem	Complexity Longer training period
XG-Boost	Easy to read and interpret	Sensitive to outliers
Recurrent neural networks (RNNs)	Model size does not increase with input size.	Slow computation
Convolutional neural networks (CNNs)	Better performance for image-related vision tasks	Requires a large-scale dataset for training

Faculty of Medicine
The Chinese University of Hong Kong

Wong GL..... Wong VW. J Gastroenterol Hepatol. 2021 Mar;36(3):543-550.

Key Takeaway: Even though AI based image analysis can give higher accuracy, they need more validations.

POSTERS

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.

Man Kit Leung et al

Objective:

To evaluate the cost-utility of PIVKA-II-based surveillance strategies (i.e., PIVKA-II + AFP, GAAD, and GAAD + US) versus standard-of-care to detect HCC in patients with compensated liver cirrhosis (CLC) or chronic hepatitis B (HepB) infection in Hong Kong.

Methods:

- Two probabilistic, micro-simulation models, which compared guideline-based surveillance of HCC with PIVKA-II-based surveillance in Hong Kong, were used with a simulated cohort of 100,000.
- Standard of care (ultrasound [US] + AFP) was compared to PIVKA-II-based surveillance strategies (i.e., PIVKA-II + AFP, GAAD, and GAAD + US) biannually.
- Model parameters for epidemiology, utility, and cost were obtained from literature and verified by clinical experts.
- Performance of PIVKA-II-based surveillance were from recent studies that include Chinese patients

Results:

One-way sensitivity analysis for net monetary benefit (NMB) was performed by varying the cost, diagnostic performance, utility and transition probabilities. NMB was calculated for a willingness to pay of HKD 400,000 per QALY gained. In this cost-utility analysis, both PIVKA-II + AFP & GAAD were dominant (i.e., less cost and better outcome) when comparing to US + AFP for both HepB and cirrhotic patients. GAAD + US was also dominant for cirrhotic patients, and considered a cost-effective option for HepB patients. All PIVKA-II-based surveillance strategies, including PIVKA-II + AFP, GAAD and GAAD + US had better ability of detecting early-stage HCC than US + AFP.

Link to poster

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

Cost-Effectiveness of Territory-wide Hepatitis B Screening Program in Hong Kong: Preliminary Results from a Pragmatic Agent-based Model

Man Kit Leung et al

Objective:
To provide actionable analysis by considering many pragmatic aspects including the primary care operation and public-private partnership in Hong Kong.

Method:
A 5-year screening program with an intervention package that includes screening and treatment with private specialists. We designed the intervention to utilize key healthcare initiatives of the Hong Kong Government: District Health Centres (DHC) and Public-Private Partnership (PPP), to approximate the actual intervention that will be rolled out in the real-world.

Outcome Measures

- Clinical measures: Changes in number of patients by disease state
- Economic measures: Total cost and total quality-adjusted life-year (QALY)
- Health system measures: Changes in outpatient visits and hospitalization days

	Cost-effectiveness results		Clinical service utilization		Complication preventions		
Partici pation	Cost saving	QALY gained	OP visits	Hosp days	# of Cirrhosis	# of DC	# of HCC
10%	40M	287	-1851	-5436	-71	-35	-63
20%	78M	583	-3666	-11031	-146	-72	-129
50%	195M	1444	-9211	-27762	-368	-178	-322
80%	313M	2312	-14655	-43524	-580	-285	-515
100%	390M	2869	-18334	-55045	-728	-357	-642

Participation, Participation ratio; QALY, Quality adjusted life year; OP visits, Outpatient visits; Hosp days, Hospitalization days; DC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma

Link to poster

Key Takeaway: Population-wide hepatitis B screening utilizing primary care infrastructure and public-private partnership in Hong Kong is cost-saving.