Changing etiology of cirrhosis and other chronic liver diseases: implications for hepatocellular carcinoma surveillance in non-cirrhotic patients
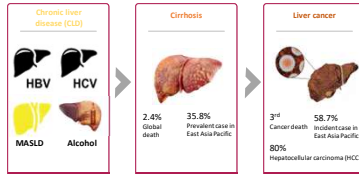
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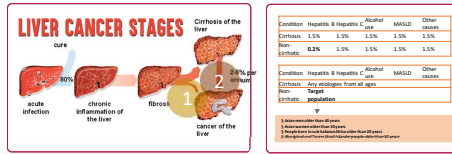
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1. Background

High burden of liver cancer in East Asia Pacific

Chronic liver disease (CLD): HBV, HCV, MASLD, Alcohol

Cirrhosis: 2.4% Global death, 35.8% Prevalent case in East Asia Pacific

Liver cancer: 3rd Cancer death, 58.7% Incident case in East Asia Pacific, 80% Hepatocellular carcinoma (HCC)

Annual HCC incidence is the indicator for the evaluation of HCC surveillance cost-effectiveness

Condition	Hepatitis B & Hepatitis C	Alcohol use	MASLD	Other causes
Cirrhosis	1.5%	1.5%	1.5%	1.5%
Non-cirrhotic	0.2%	1.5%	1.5%	1.5%

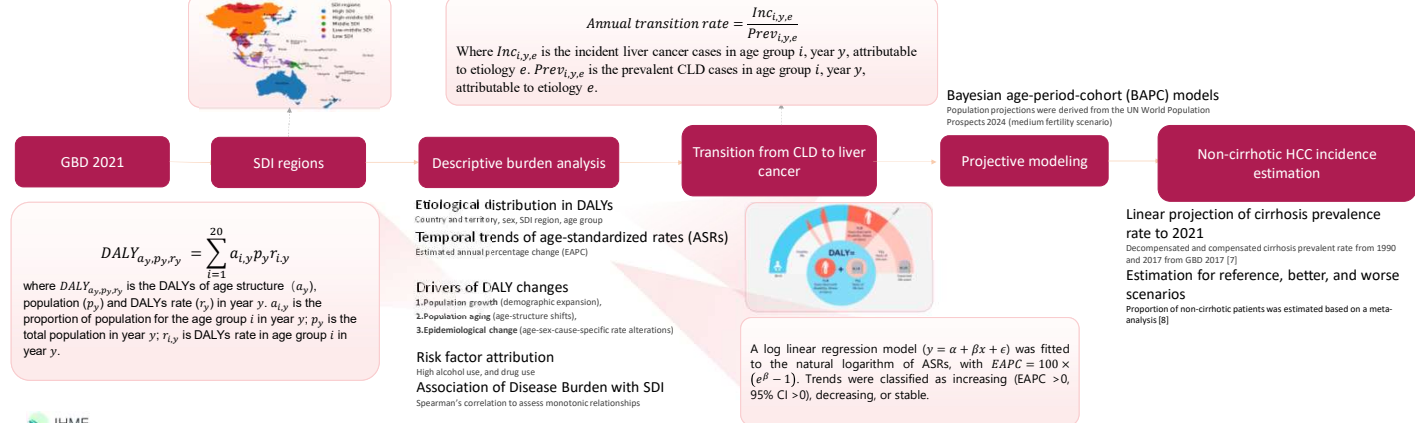| Condition	Hepatitis B & Hepatitis C	Alcohol use	MASLD	Other causes
Cirrhosis	Any etiologies from all ages			
Non-cirrhotic	Target population			

Lack of consensus on HCC surveillance in non-cirrhotic patients

Country	Chronic HBV	Chronic HCV	MASLD	Other conditions	Reference
Australia	√				[1]
China	√	√			[2]
Japan	√	√			[3]
Malaysia	√			Family history of HCC	[4]
Philippines	√			Family history of HCC, males aged 40 years and above, and females aged 50 years and above	[5]
South Korea	√	√			[6]

2. Methods

$$Annual\ transition\ rate = \frac{Inc_{i,y,e}}{Prev_{i,y,e}}$$

Where $Inc_{i,y,e}$ is the incident liver cancer cases in age group i, year y, attributable to etiology e. $Prev_{i,y,e}$ is the prevalent CLD cases in age group i, year y, attributable to etiology e.

Bayesian age-period-cohort (BAPC) models
Population projections were derived from the UN World Population Prospects 2024 (medium fertility scenario)

GBD 2021 → SDI regions → Descriptive burden analysis → Transition from CLD to liver cancer → Projective modeling → Non-cirrhotic HCC incidence estimation

$$DALY_{a_y,p_y,r_y} = \sum_{i=1}^{20} a_{i,y} p_y r_{i,y}$$

where $DALY_{a_y,p_y,r_y}$ is the DALYs of age structure (a_y), population (p_y) and DALYs rate (r_y) in year y. $a_{i,y}$ is the proportion of population for the age group i in year y; p_y is the total population in year y; $r_{i,y}$ is DALYs rate in age group i in year y.

Etiological distribution in DALYs — Country and territory, sex, SDI region, age group

Temporal trends of age-standardized rates (ASRs) — Estimated annual percentage change (EAPC)

Drivers of DALY changes
1. Population growth (demographic expansion),
2. Population aging (age-structure shifts),
3. Epidemiological change (age-sex-cause-specific rate alterations)

Risk factor attribution — High alcohol use, and drug use

Association of Disease Burden with SDI — Spearman's correlation to assess monotonic relationships

A log linear regression model ($y = \alpha + \beta x + \epsilon$) was fitted to the natural logarithm of ASRs, with $EAPC = 100 \times (e^{\beta} - 1)$. Trends were classified as increasing (EAPC >0, 95% CI >0), decreasing, or stable.

Linear projection of cirrhosis prevalence rate to 2021 — Decompensated and compensated cirrhosis prevalent rate from 1990 and 2017 from GBD 2017 [7]

Estimation for reference, better, and worse scenarios — Proportion of non-cirrhotic patients was estimated based on a meta-analysis [8]

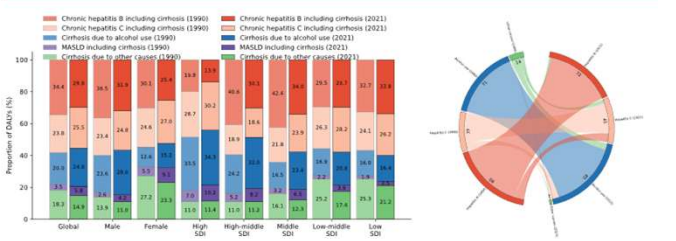IHME — Data source: Global Burden of Disease 2021 (GBD 2021)

3. Results
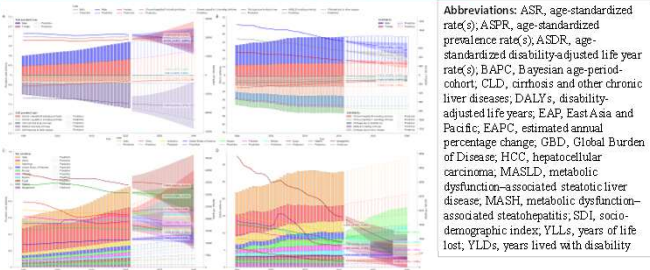
A marked decline in age-standardized DALY rates for chronic liver disease across all etiologies was observed in East Asia and Pacific

Etiology:
- Chronic hepatitis B including cirrhosis
- Chronic hepatitis C including cirrhosis
- Cirrhosis due to alcohol use
- MASLD including cirrhosis
- Cirrhosis due to other causes

DALYs distribution in 2021

World bank regions:
- East Asia and Pacific
- Europe and Central Asia
- Latin America and Caribbean
- Middle East and North Africa
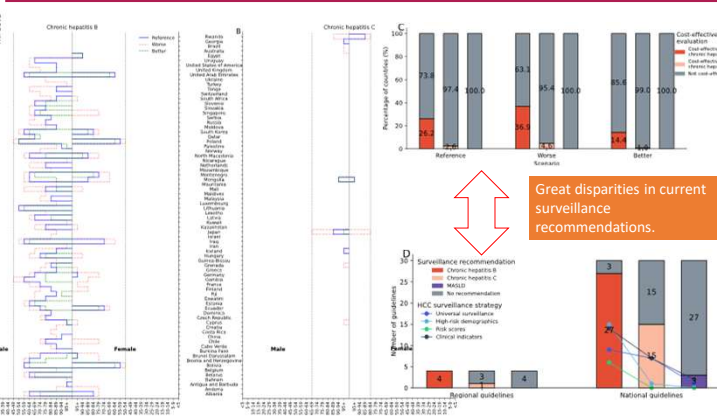- North America
- South Asia
- Sub-Saharan Africa

The proportion of chronic liver disease (CLD) DALYs attributable to alcohol use and MASLD increased across both sexes and all SDI regions. Notably, alcohol use emerged as the leading etiology of CLD DALYs in 50% of countries.

The cost-effectiveness of surveillance among non-cirrhotic patients was estimated at 26.2% for hepatitis B, 2.6% for hepatitis C, and 0% for MASLD. The cost-effectiveness threshold for initiating surveillance varied significantly by country.

Great disparities in current surveillance recommendations.

By 2040, MASLD is projected to account for 81.5% of the global prevalence of CLD

Abbreviations: ASR, age-standardized rate(s); ASPR, age-standardized prevalence rate(s); ASDR, age-standardized disability-adjusted life year rate(s); BAPC, Bayesian age-period-cohort; CLD, cirrhosis and other chronic liver diseases; DALYs, disability-adjusted life years; EAP, East Asia and Pacific; EAPC, estimated annual percentage change; GBD, Global Burden of Disease; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; SDI, socio-demographic index; YLLs, years of life lost; YLDs, years lived with disability
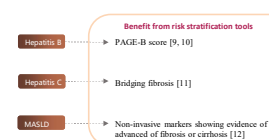
4. Discussion

Although progress in controlling hepatitis B and C is reflected in the declining ASDR of CLD, the rising impact of MASLD and alcohol-related liver disease demands urgent attention

Hepatitis B and C — Effective control but still dominant in DALYs
- Targeted vaccination campaigns in hepatitis B: South Korea, Singapore, and China
- Antiviral therapies of hepatitis C
- Out-of-hospital births and vaccine hesitancy impede timely vaccination

MASLD — Fastest growing and dominate in prevalence
- increasing obesity rates, unhealthy diets, and sedentary lifestyles
- Public health initiatives promoting healthy diets, physical activity, and obesity awareness are vital

Alcohol use — Severe in high SDI regions
- alcohol taxation, public health campaigns, and support programs for reducing alcohol dependency
- Cultural and social factors, such as stress and lifestyle changes

HCC surveillance in non-cirrhotic patients may not be broadly cost-effective, underscoring the need to refine surveillance guidelines

Benefit from risk stratification tools
- Hepatitis B → PAGE-B score [9, 10]
- Hepatitis C → Bridging fibrosis [11]
- MASLD → Non-invasive markers showing evidence of advanced of fibrosis or cirrhosis [12]

5. Conclusion

Changing epidemiology of CLD
HBV and HCV burden have been reduced. MASLD and alcohol-related liver diseases is rising.

Efforts needed for the reduction of CLD burden
Expanded vaccination programs, greater access to antiviral therapies, and public health initiatives targeting obesity and alcohol consumption

High transition rate from CLD to liver cancer
The transition in EAP was higher in all etiologies than the global rate.

HCC surveillance in non-cirrhotic patients may not be broadly cost-effective
The need to refine surveillance guidelines and use risk stratification tools to identify populations at risk who are likely to benefit from HCC surveillance. Developing and validating effective risk stratification tools

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