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MEETING SUMMARY
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HEPATOCELLULAR CARCINOMA

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COMBINED METHYLATED DNA AND PROTEIN MARKERS: AN ACCURATE BLOOD-BASED TEST FOR EARLY-STAGE DETECTION OF HEPATOCELLULAR CARCINOMA

Chalasani NP, et al. AASLD 2019 Abstract #109

AIM AND METHODS

- High performing blood-based markers are needed for early detection of HCC, as liver ultrasound and serum AFP have suboptimal sensitivity
- **Aim**: to identify a panel of methylated DNA markers (MDMs) and proteins to detect early-stage HCC[1]
- **Methods**
  - Blood samples were collected from patients with radiographically diagnosed HCC and age-matched controls with benign liver disease without structurally apparent HCC
  - 10 previously reported MDMs[2] and multiple candidate proteins, including AFP, were assessed at a central laboratory
  - A logistic regression algorithm was developed to make HCC-positive or -negative calls
  - The accuracy of the MDM and protein panel was compared to AFP alone
  - Data were analysed across all BCLC stages, early-stage HCC (stages 0 and A) and excluding stage 0 due to its diagnostic uncertainty

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MDM, methylated DNA marker

1. Chalasani NP, et al. AASLD 2019 Abstract #109. 2. Kisiel JB, et al. Hepatology 2019;69:1180-92

RESULTS

- 137 patients with HCC and 313 controls
  - 73 early-stage HCC cases and and 64 BCLC stages B-D cases
- With specificity set at 90%, a **panel of 4 MDMs and 2 protein markers** (AFP and lectin-bound AFP) was determined

Sensitivity of a 6-marker panel and AFP 20 ng/mL for hepatocellular carcinoma

	Early-stage positives (N=73)	Early-stage sensitivity (95% CI)	Total positives (N=137)	All-stage sensitivity (95% CI)	Specificity
6-marker panel	52	71.2% (59.4–81.2%)	110	80.3% (72.6–86.6%)	90.0%
AFP 20 ng/mL	18	24.7% (15.3–36.1%)	58	42.3% (33.9–51.1%)	97.4%

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; MDM, methylated DNA marker
Chalasani NP, et al. AASLD 2019 Abstract #109

AUTHORS' CONCLUSIONS AND INTERPRETATION

- A panel of 4 MDMs and 2 proteins demonstrated **high sensitivity for early-stage HCC**
- These data support the near-term potential for improved performance of blood-based testing for HCC
  - This could have substantial clinical implications on the effectiveness of disease management and patient outcomes

Although the study design might have caused an overestimation of the performance of this panel, these results are exciting and warrant further validation in future studies

HCC, hepatocellular carcinoma; MDM, methylated DNA marker

Chalasani NP, et al. AASLD 2019 Abstract #109

THE IMPACT OF HEALTHY LIFESTYLE ON THE INCIDENCE OF HEPATOCELLULAR CARCINOMA AND CIRRHOSIS-RELATED MORTALITY AMONG U.S. ADULTS

Simon TG, et al. AASLD 2019 Abstract #16

METHODS

- Little is known about the shared impact of lifestyle on major hepatic outcomes
  - The proportion of incident HCC cases and cirrhosis-related deaths that might be prevented by adopting a healthy lifestyle are unknown
- This **nationwide, prospective cohort study** included adults without known liver disease at baseline
  - Detailed clinical, lifestyle and dietary data were collected biennially from 1986-2012
  - All incident HCC cases and deaths were confirmed

Low-risk lifestyle group

1. Never/prior smoking (pack years <5)
2. No/moderate alcohol use (<1 drink/day [women], <2 drinks/day [men])
3. BMI 18.5-24.9 kg/m^2
4. Weekly physical activity ≥6 MET hours
5. Healthy diet (upper 40% of the AHEI)

High-risk lifestyle group

Any subject not meeting all 5 criteria of the low-risk lifestyle group

AHEI, Alternative Healthy Eating Index; HCC, hepatocellular carcinoma; MET, metabolic equivalent task

Simon TG, et al. AASLD 2019 Abstract #16

RESULTS

- 121,893 adults were followed for 2,388,811 person years
- 121 incident HCC cases and 350 cirrhosis-related deaths were confirmed
- The single modifiable risk factor was overweight/obesity

Healthy lifestyle score	Age-adjusted incidence, per 100,000 person-years		Adjusted PAR, % (95% CI)
	Low-risk group	*High-risk group*	*Low-risk vs. high-risk group*[a]
Pooled cohort			
• Incident HCC	2	7	90 (56–98)
• Liver-related mortality	5	17	89 (43–98)
Women			
• Incident HCC	2	6	91 (34–99)
• Liver-related mortality	6	16	69 (34–88)
Men			
• Incident HCC	3	7	88 (21–99)
• Liver-related mortality	5	17	87 (59–96)

[a] Calculated using the %PAR macro, with adjustment for age (continuous years), sex, race/ethnicity, diabetes, hypertension, dyslipidaemia, statin use and regular aspirin use (i.e. ≥ 325 mg weekly dose, taken >2 times per week)

CI, confidence interval; HCC, hepatocellular carcinoma; PAR, population attributable risk

Simon TG, et al. AASLD 2019 Abstract #16

AUTHORS' CONCLUSIONS AND INTERPRETATION

- A substantial burden of HCC and cirrhosis-related mortality may be **prevented by lifestyle modification**
- Developing effective strategies to prevent incident HCC and cirrhosis-related mortality should remain a high priority

Healthy lifestyle can markedly reduce the incidence of HCC and cirrhosis-related mortality

HCC, hepatocellular carcinoma
Simon TG, et al. AASLD 2019 Abstract #16

DIRECT-ACTING ANTIVIRAL THERAPY IS ASSOCIATED WITH IMPROVED SURVIVAL IN PATIENTS WITH A HISTORY OF HEPATOCELLULAR CARCINOMA: A MULTICENTER NORTH AMERICAN COHORT STUDY

Singal AG, et al. AASLD 2019 Abstract #199

METHODS

- There is uncertainty over the benefits of direct-acting antiviral (DAA) therapy for HCV infection in patients with a history of HCC

- This **retrospective cohort study** compared overall survival between DAA-treated and untreated HCV-infected patients who achieved a complete response to HCC treatment in a North-American cohort
  - Included patients with a complete response to resection, local ablation, TACE, TARE or radiation therapy

HCC, hepatocellular carcinoma; HCV, hepatitis C; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation

Singal AG, et al. AASLD 2019 Abstract #199

RESULTS

N = 797	DAA therapy	Untreated	Crude rate ratio (95% CI)
n (%)	383 (48.1)	414 (51.9)	
Deaths, n/person-years of follow-up	43/941	103/527	0.23 (0.16-0.33)
Median time from HCC CR to death, months (IQR)	25.7 (19.4-33.9)	11.5 (7.1-20.2)	

- **DAA therapy was associated with significantly reduced mortality** in multivariable analyses[a] (HR 0.39, 95% CI 0.26-0.61) and a propensity score model (HR 0.55, 95% CI 0.31-0.97)
  - This association appeared to be **driven by SVR**, with reduced mortality observed in DAA-treated patients who achieved SVR (HR 0.26, 95% CI 0.16-0.42) but not in those without SVR (HR 0.78, 95% CI 0.40-1.52)
- There was a greater benefit of DAA therapy in patients who remained HCC **recurrence-free** (HR 0.09, 95% CI 0.02-0.34) compared with those who experienced recurrence (HR 0.62, 95% CI 0.37-1.04) (p=0.01)

[a] Multivariable analysis adjusted for study site, age, sex, Child Pugh score, alpha-fetoprotein level, tumour burden and HCC treatment modality

CI, confidence interval; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; SVR, sustained viral response

Singal AG, et al. AASLD 2019 Abstract #199

AUTHORS' CONCLUSIONS AND INTERPRETATION

- In a large cohort of North-American patients with complete response to HCC treatment, **DAA therapy was associated with significantly reduced mortality**

DAA therapy has benefit in HCV-infected patients with a history of HCC and should be considered to improve prognosis

DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus
Singal AG, et al. AASLD 2019 Abstract #199

GROWTH RATES OF UNTREATED HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CIRRHOSIS: A MULTICENTER COHORT STUDY

Rich NE, et al. AASLD 2019 Abstract #842

METHODS

- **Retrospective multicentre cohort study** of cirrhosis patients diagnosed with HCC from 2008-2017 in the USA
  - Meeting imaging criteria for HCC (LI-RADS 5 as defined per AASLD guidelines and LI-RADS v.2018)
  - ≥2 contrast-enhanced imaging studies performed ≥30 days apart prior to HCC treatment
- **Aim:** to quantify tumour growth rates and identify clinical correlates of indolent tumour growth
- All tumours were re-measured in 3 dimensions by fellowship-trained radiologists
  - For patients with multiple tumours, the single largest tumour was measured
  - Results were validated in an independent cohort from 2 centres (USA and UK)

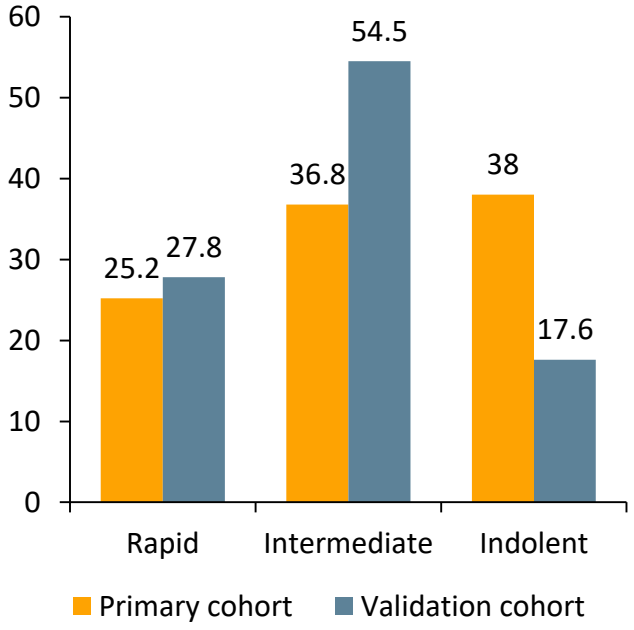
AASLD, American Association for the Study of Liver Diseases; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System

Rich NE, et al. AASLD 2019 Abstract #842

RESULTS

Tumour growth rates[a]	Primary cohort (N = 242)				Validation cohort (n=176)
	Total	Indolent growth	Intermediate growth	Rapid growth	
n (%)	242 (100)	92 (38.0)	89 (36.8)	61 (25.2)	
Median TDT, days (IQR)	229 (89-627)	1386 (526-2310)	181 (136-266)	53 (44-76)	169 (74-408)
Median SGR, %/day (IQR)	0.3 (0.1-0.8)				0.4

- There was an **inverse relationship between tumour size and TDT**
  - Median TDT of 6.1, 7.2, and 13.6 months for initial HCC diameter 1-2 cm, 2-5 cm, and >5 cm, respectively (p=0.04)
- In multivariable analysis, **indolent growth** was
  - associated with **larger HCC diameter** (OR 1.15, 95% CI 1.03-1.30)
  - **inversely** associated with **AFP >20 ng/mL** (OR 0.60, 95% CI 0.37-0.98)
  - associated with **non-viral cirrhosis in T1 HCC** (OR 3.41, 95% CI 1.08-10.80)



[a] indolent (TDT >365 days), intermediate, (TDT 90-365 days), or rapid (TDT <90 days) growth, based on clinically relevant cut-offs determined a priori

AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular carcinoma; IQR, interquartile range; OR, odds ratio; SGR, specific growth rate; TDT, tumour doubling time

Rich NE, et al. AASLD 2019 Abstract #842

AUTHORS' CONCLUSIONS AND INTERPRETATION

- In a large Western cohort of HCC patients, tumour **growth rates varied significantly**
  - Over one third of was classified as indolent
- **Indolent growth** was more common in **non-viral cirrhosis and larger tumours**, while smaller tumours exhibited more rapid growth
- These data may help guide future efforts towards HCC surveillance and treatment

Although HCC is usually regarded to be an aggressive cancer, this study shows significant variation in the growth rates of hepatocellular tumours. This heterogeneity may have implications for many aspects of HCC care, from surveillance to treatment

HCC, hepatocellular carcinoma
Rich NE, et al. AASLD 2019 Abstract #842

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