AASLD
Nov. 12–15, 2021

The Liver Meeting®

DIGITAL EXPERIENCE

The Best of The Liver Meeting®

LIVER CANCER

About the program:

Best of The Liver Meeting 2021 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

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HCC incidence threshold for routine surveillance is much lower in hepatitis C cirrhosis individuals who achieve virological cure

Objective

- The AASLD guidance recommends biannual surveillance for (HCC) in individuals with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY); however, this threshold is unknown for individuals **who achieved virological cure**. Our objective was to estimate this HCC incidence threshold in cirrhosis patients.

Methods

- A microsimulation model of the natural history of HCC in individuals with HCV and cirrhosis who achieved virological cure with oral direct-acting antivirals (DAAs)

Main Findings

- Using the recommended willingness to pay threshold of $100,000 per quality-adjusted life year, HCC surveillance could be cost-effective if the annual incidence rate of HCC exceeds 0.41%, which is much lower than the previous 1.5% incidence used to guide HCC surveillance decisions

Conclusions

- Our study provides an important update on HCC incidence threshold above which routine HCC surveillance is cost-effective in individuals with HCV cirrhosis who achieved cure with DAAs.

Chhatwal J, et al., Abstract 28.
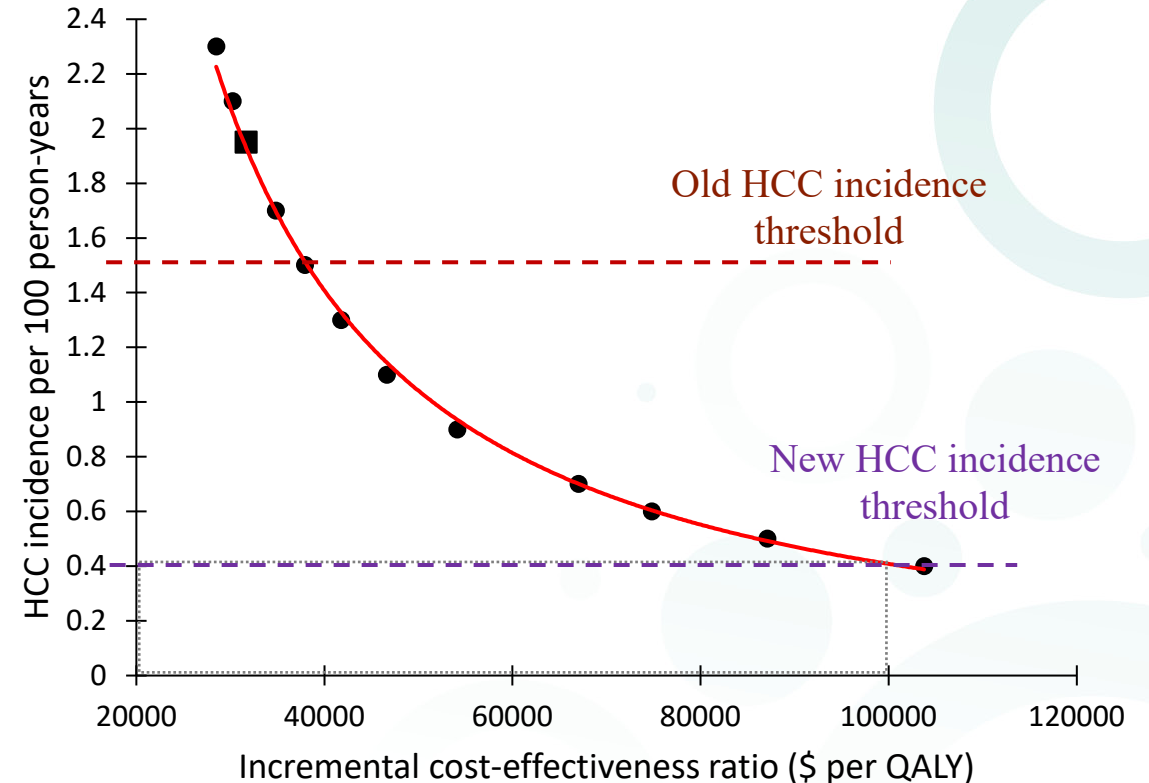
Multi-center randomized clinical trial of a mailed outreach strategy for hepatocellular carcinoma surveillance

Aim: Evaluate the effectiveness of a mailed outreach program to promote hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis

Methods: Multi-center pragmatic randomized clinical trial comparing mailed outreach for surveillance ultrasound (n=1436) and usual care with visit-based surveillance (n=1436) in patients with cirrhosis at three health systems from April 2018 to December 2019
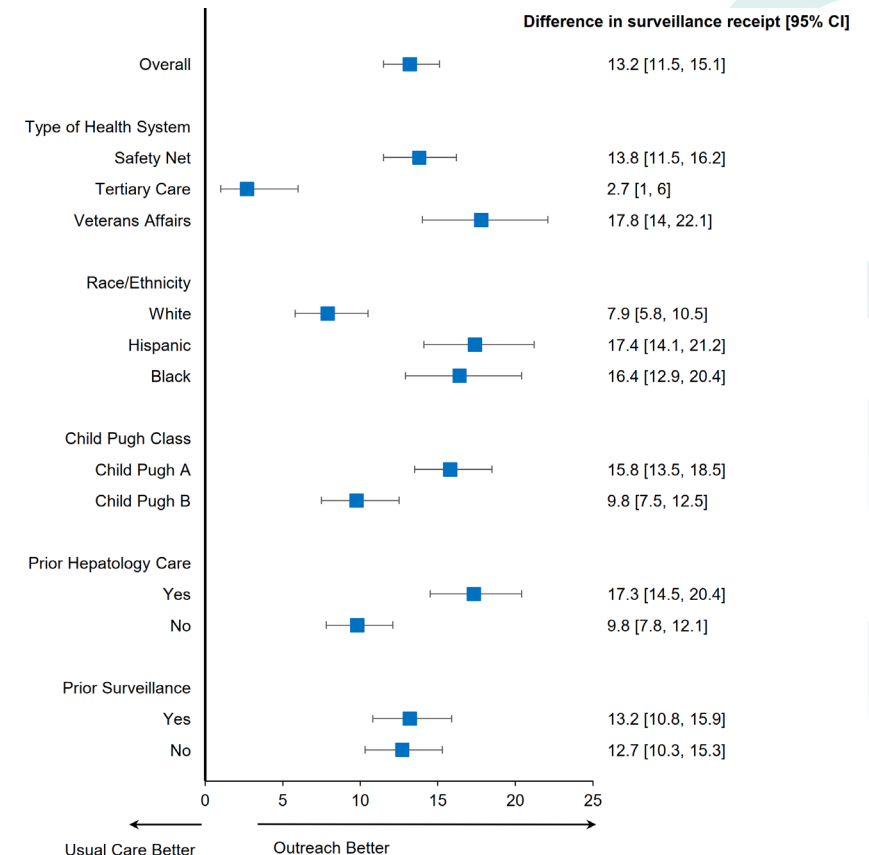
- Primary outcome was guideline concordant semi-annual HCC surveillance over a 12-month period

Main Findings: Compared to usual care, the outreach arm had significantly higher semi-annual surveillance (35.1% vs. 21.9%), resulting in increases in the proportion of time covered by surveillance (41.3% vs. 31.0%, p<0.001)

- The intervention increased HCC surveillance across most predefined subgroups; however, there were site-level differences in the intervention effect (**Figure**)

Conclusions: Mailed outreach invitations significantly increased semi-annual HCC surveillance versus usual care in patients with cirrhosis, with a consistent intervention effect across most examined subgroups.

Singal A, et al., Abstract 133.

Difference in surveillance receipt [95% CI]

Overall	13.2 [11.5, 15.1]
Type of Health System	
Safety Net	13.8 [11.5, 16.2]
Tertiary Care	2.7 [1, 6]
Veterans Affairs	17.8 [14, 22.1]
Race/Ethnicity	
White	7.9 [5.8, 10.5]
Hispanic	17.4 [14.1, 21.2]
Black	16.4 [12.9, 20.4]
Child Pugh Class	
Child Pugh A	15.8 [13.5, 18.5]
Child Pugh B	9.8 [7.5, 12.5]
Prior Hepatology Care	
Yes	17.3 [14.5, 20.4]
No	9.8 [7.8, 12.1]
Prior Surveillance	
Yes	13.2 [10.8, 15.9]
No	12.7 [10.3, 15.3]

Usual Care Better ← → Outreach Better

Incidence and clinical characteristics of hepatocellular carcinoma associated with non-alcoholic fatty liver disease without cirrhosis or advanced liver fibrosis

Aim

- Hepatocellular carcinoma (HCC) usually occurs in cirrhotic livers but can develop in the absence of cirrhosis in NAFLD patients

- We aimed to estimate the incidence of HCC in NAFLD with and without cirrhosis or advanced liver fibrosis

Methods

- Retrospective case-control analysis of 47,970 NAFLD patients between 40-89 years of age, stratified by cirrhosis and by Fibrosis-4 index (FIB-4)

Main Findings

- 755 (1.6%) of 47,970 NAFLD patients developed HCC with an average 3.5 years of follow-up, resulting in annual rate at 0.46% (Table 1).

- Incidence rate of HCC in patients with cirrhosis was 1.94% and 0.16% in those without cirrhosis.

- Among patients without cirrhosis, HCC incidence rate was 0.6% for FIB-4 > 2.67 and 0.09% for FIB-4 < 1.3.

- HCC-NAFLD patients without cirrhosis had different characteristics (Table 2).

Conclusions

- NAFLD patients without cirrhosis or advanced fibrosis have low incidence of HCC but exhibit different clinical characteristics.

Behari J, et al., Abstract 134.

Table 1. Distribution of cirrhosis and FIB-4 scores among NAFLD patients with or without HCC and corresponding annual incidence rate of HCC.

	HCC N (%)	Non-HCC N (%)	Annual incidence rate of HCC (%)
All subjects	755 (100)	47,215 (100)	0.46%
Diagnosis of cirrhosis			
Yes	528 (69.9)	7,009 (14.8)	1.94%
No	227 (30.1)	40,206 (85.2)	0.16%
FIB-4 score among subjects without cirrhosis			
<1.30	55 (7.3)	18,760 (39.7)	0.09%
1.30-2.67	67 (8.8)	11,812 (25.0)	0.15%
>2.67	68 (9.0)	3,529 (7.5)	0.60%
Unknown	37 (4.9)	6,105 (12.9)	0.22%

Table 2. Characteristics of HCC patients with and without cirrhosis by FIB-4

	HCC with cirrhosis	HCC without cirrhosis			
		All	FIB-4<1.30	1.30-	>2.67
N	528	227#	55	67	68
Age (year)**	68.5	66.7	59.1	68.3	71.2
BMI (kg/m²)	31.1	31.9	31.6	32.3	31.3
AST (U/L)**	88.0	57.7	26.4	44.3	97.7
ALP (U/L)^	188.2	159.6	133.9	160.1	182.3
Albumin (g/dL)**	3.28	3.57	3.69	3.60	3.42
Platelet (x10³/ μL)^	173.0	227.7	324.7	222.1	154.8
Total bilirubin (mg/dL)**	2.21	1.10	0.89	0.88	1.55
Hyperlipidemia (%)^	28.3	36.6	45.5	47.8	36.8

*P<0.05 for difference between HCC with cirrhosis and without cirrhosis. ^P<0.05 for difference between FIB-4 groups among HCC without cirrhosis; # 37 cases with missing FIB-4 data were excluded from the analysis.

Prospective surveillance of patients with primary sclerosing cholangitis for early detection of cholangiocarcinoma

Aim

- To prospectively evaluate cholangiocarcinoma (CCA) surveillance with yearly magnetic resonance imaging with cholangiopancreatography (MRI/MRCP) in a nation-wide cohort study

Methods

- Prospective 5-year surveillance study with yearly MRI/MRCP, clinical evaluations and liver function tests in patients with primary sclerosing cholangitis (PSC). Patients with worrisome features on MRI/MRCP were further investigated.

Main Findings

- The incidence of CCA was 2% (11/512).

- 24% (122/512) developed worrisome features but only 10% had underlying malignancy.

- The median survival for patients with CCA was 13 months (3-22 months).

Conclusions

- MRI/MRCP surveillance followed by standard investigations did not detect cancer early enough to provide long-term survival. This together with very low occurrence of CCA question the value of yearly MRI/MRCP surveillance in all PSC patients.
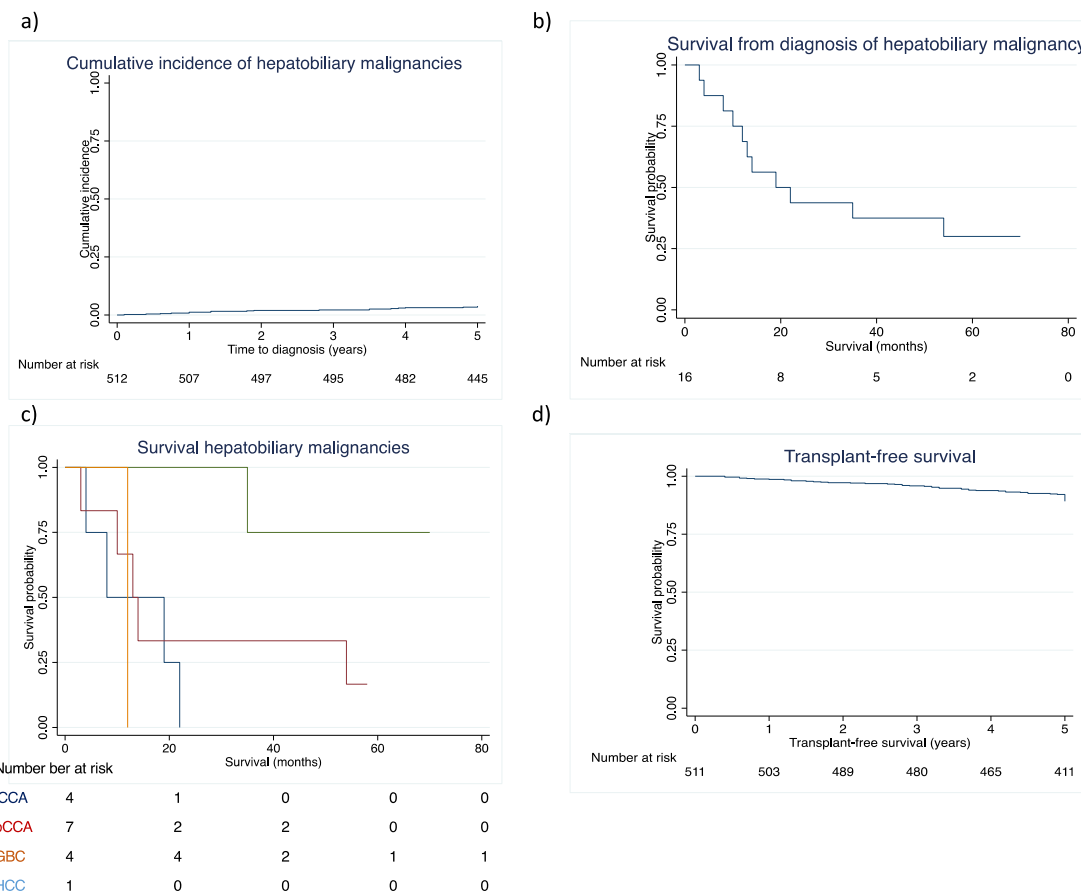
Villard C, et al., Abstract 136.

GALAD score improves early detection of HCC prior to the diagnosis of HCC: a phase 3 biomarker validation study

Aims

- To compare the performance of AFP and GALAD for the detection of HCC

- To determine the performance of AFP and GALAD in those who underwent surveillance by US or CT/MRI

Methods

- A phase 3 biomarker validation study-HEDS study.

- Prospective cirrhosis cohort study of 1559 patients

- GALAD tested blindly at diagnosis and 6 months prior to HCC diagnosis.

Main Findings

- GALAD had the best performance of any biomarker at HCC diagnosis and 6 months prior to HCC diagnosis.

- GALAD can potentially limit unnecessary diagnostic CT or MRI.

Conclusions

- GALAD has better performance characteristics 6 months prior to HCC diagnosis and at the time of HCC diagnosis.

Marrero J, et al., Abstract 138.

	DCP	AFP-L3	AFP	GALAD
Threshold	2.82	6.35%	9.12	- 0.76 score
AUC	0.79	0.66	0.68	0.81
Sensitivity	44%	38%	33%	54%
Specificity (fixed 90%)	90%	90%	90%	90%

TLMdX®

Multiomics profiling identifies the pro-tumoral immune networks in the steatotic tumor microenvironment in non-viral hepatocellular carcinoma

Aim To clarify molecular and immunological abnormalities in non-viral HCCs by omics approach

Methods

- We performed RNA-sequence of tumor tissues in 113 non-viral HCC patients who underwent curative surgical resection.

- For 55 tumors, we further sequenced cancer genomes using gene panels focusing on 68 genes in which recurrent genetic alterations were reported in HCC.

Conclusions

Multiomics profiling identified the pro-tumor immune subclass in non-viral HCCs and suggested the link between intratumor steatosis and pro-tumor immune microenvironment.

Murai H, et al., Abstract 195.
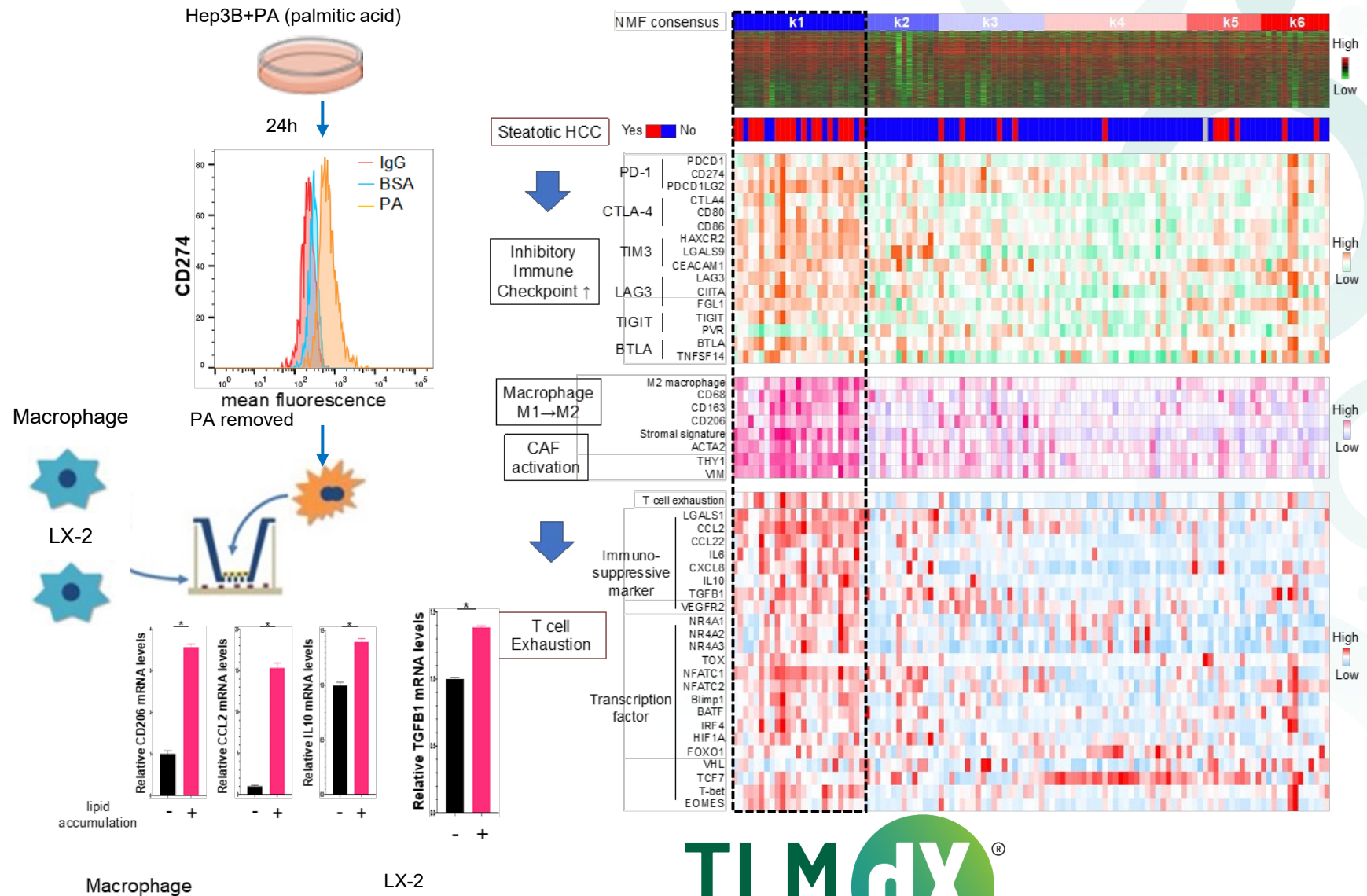
A blood-based prognostic liver secretome signature for long-term HCC risk prediction and chemopreventive intervention

Aim

To identify a blood-based secretome signature to predict long-term HCC risk and to monitor chemopreventive intervention in patients with advanced liver fibrosis
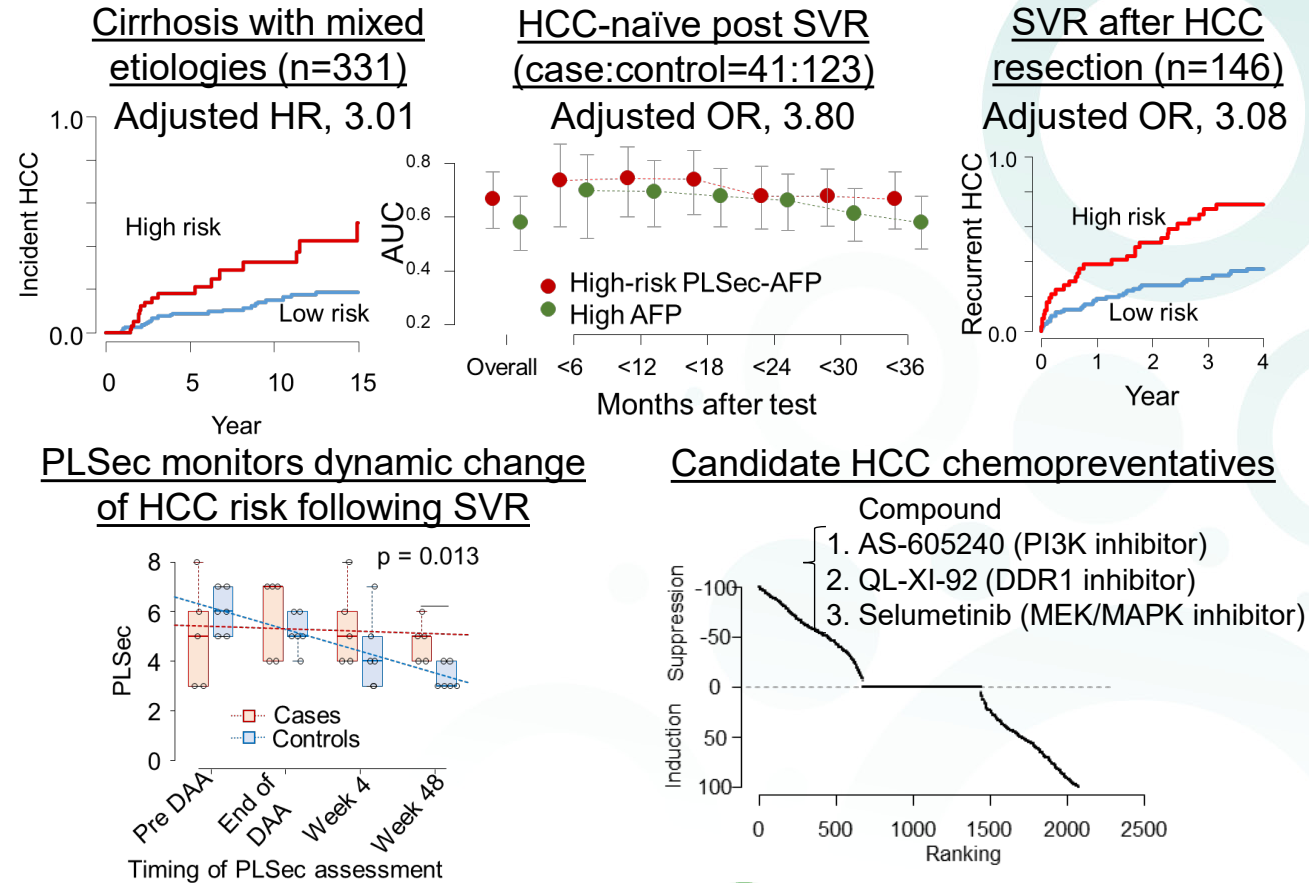
Methods

A serum protein-based signature, PLSec, was identified from previously validated hepatic transcriptome signature using our bioinformatic pipeline, TexSEC, and independently validated for its association with long-term HCC risk in three clinical scenarios (cirrhosis patients from mixed etiologies, HCC-naïve patients post sustained virologic response [SVR] by direct-acting agents [DAA], and HCC-experienced patients post SVR by DAA) as well as monitoring chemopreventive intervention.

Conclusions

The 8-protein PLSec, including IL-6, gp130, CCL-21, IGFBP-7, MMP-7, VCAM-1, Angiogenin, and Protein S, can stratify patients with advanced liver fibrosis for long-term HCC risk and may serve as a companion biomarker for chemopreventive intervention.

Fujiwara N, et al., Abstract 196.

Cirrhosis with mixed etiologies (n=331)
Adjusted HR, 3.01

HCC-naïve post SVR (case:control=41:123)
Adjusted OR, 3.80

SVR after HCC resection (n=146)
Adjusted OR, 3.08

PLSec monitors dynamic change of HCC risk following SVR

Candidate HCC chemopreventatives

Compound
1. AS-605240 (PI3K inhibitor)
2. QL-XI-92 (DDR1 inhibitor)
3. Selumetinib (MEK/MAPK inhibitor)

TLMdX®

A novel stroma, tumor, immune microenvironment-based classification of intrahepatic cholangiocarcinoma (iCCA)

Objective

- To generate a novel molecular classifier of iCCA that incorporates elements of the **S**troma, **T**umor, and **I**mmune **M**icroenvironment ("**STIM**" classification).

Methods

- Virtual deconvolution of bulk expression data from 464 iCCAs was performed to devise a novel tumor microenvironment-based classification.
- Four murine models (KRAS/p19, NICD1/AKT1, YAP1/AKT1, FBXW7/AKT1) were generated through hydrodynamic tail vein injection (HTVI) and their molecular (RNA-seq) and immune composition (CytOF and FACS) compared to the human disease.

Main Findings

- We identified five robust **STIM** classes encompassing both Inflamed (35%) and non-inflamed profiles (65%) (Figure panel **A**).
- The Inflamed classes differ in oncogenic pathways and extent of desmoplasia, with the *Inflammatory Stroma* showing CD8 T cell exhaustion and abundant stroma associated with a TGFb-related program.
- Among the Non-Inflamed classes, the *Desert-like* harbors the lowest immune infiltration whereas the *Hepatic Stem-like* class is enriched in 'M2-like' macrophages, and mutations in *IDH1/2* and *BAP1*. The *Tumor Classical* is defined by cell cycle pathways and poor prognosis.
- Cross-species analysis established that the KRAS/p19 murine model closely aligns to the human *Inflammatory Stroma* whereas NICD1/AKT1 and YAP1/AKT1 mostly resemble the *Hepatic Stem-like class* (Figure panel **B**).

Conclusions

- The proposed classification provides insights into the rational design of therapeutic strategies targeting both the cancer cells and the surrounding microenvironment, and shed light on which murine models best recapitulate the different human subtypes of iCCA for future functional studies testing combination therapies.

Sia D, et al., Abstract 197.
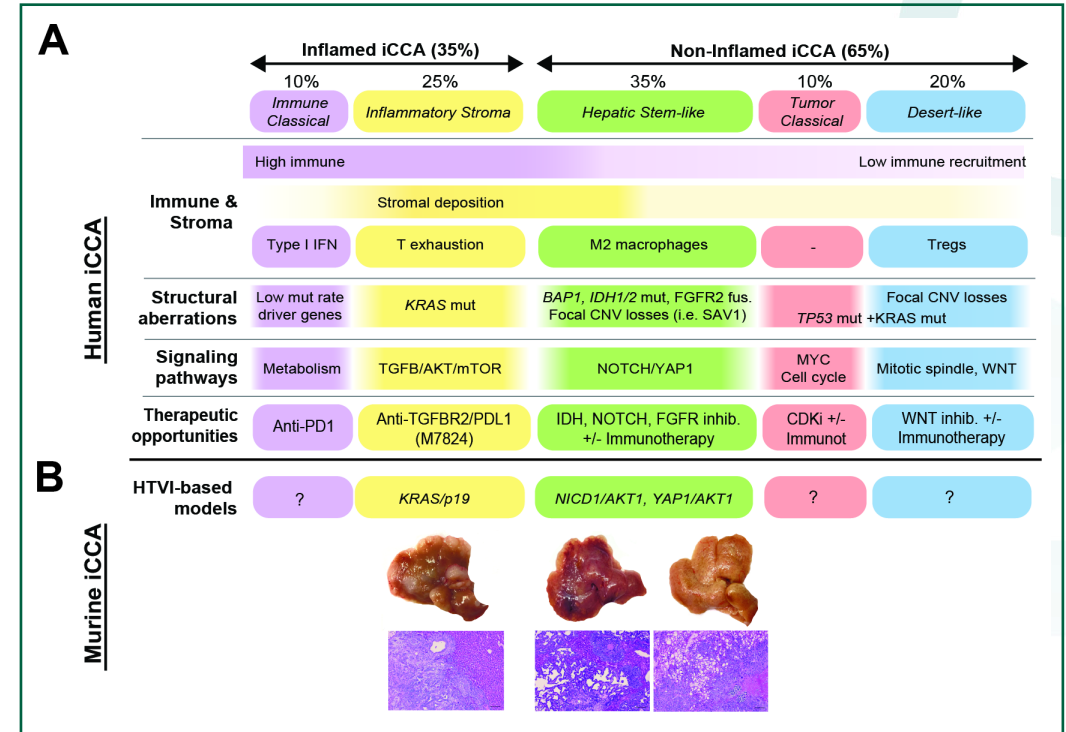
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