AASLD November 13-16, 2020
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THE BEST OF THE LIVER MEETING® 2020

# Liver and Biliary Cancer

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

## About the program:

*Best of The Liver Meeting 2020* 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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## Use of these slides:

# Mast cell-derived histamine regulates cholangiocarcinoma (CCA) phenotypes in human CCA and novel 3D culture spheroids via TMEM173/STING

## Aim

To determine the role of HA-regulated STING in intra- and extra-hepatic CCA using 3D spheroid tumors

## Methods

**Cell combinations in 3D culture**

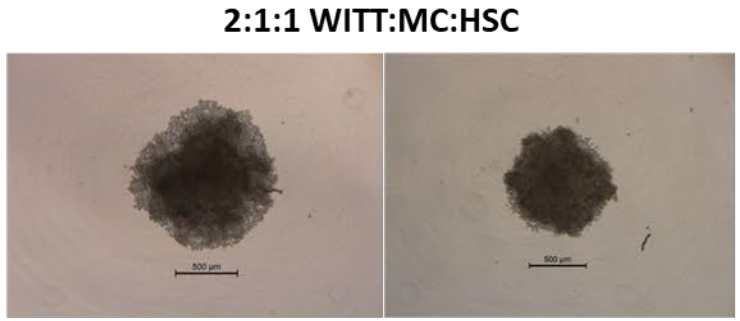
- Human CCA cells: SG231 or Witt (Mz-ChA-1)
- Human Hepatic stellate cells (HSCs)
- Human Mast cells (MCs)

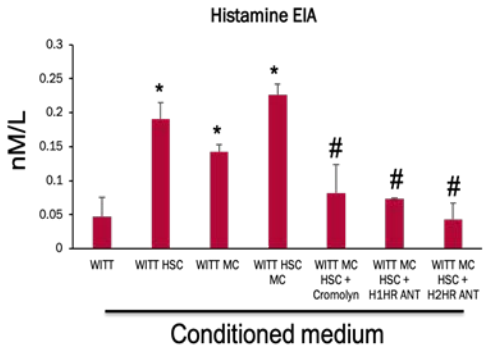
**3D culture spheroids treatments (24 hrs):**

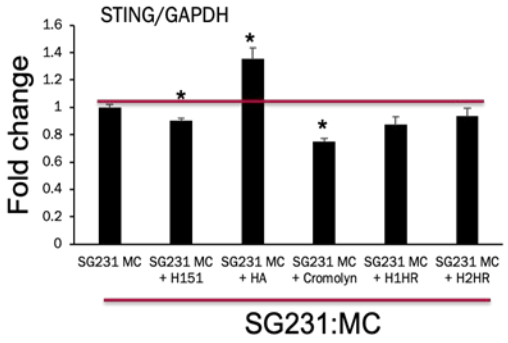
- STING inhibitor (H151)
- Histamine (HA)
- Cromolyn (mast cell stabilizer)
- Mepyramine (H1HR antagonist)
- Ranitidine (H2HR antagonist)

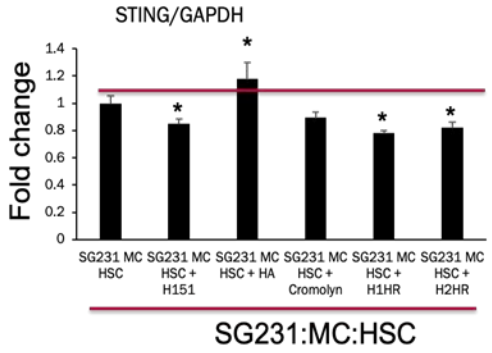
## Main Findings

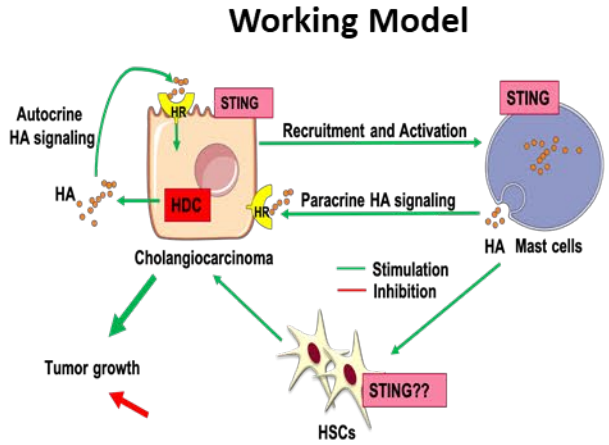
- 3D Human Spheroids Secrete Histamine
- Blocking Histamine/H1 H2R Signaling Decreases STING Expression in 3D Human SG231 Spheroids




## Conclusion

Inhibition of MCs/HA/HR signaling or STING directly decreases tumorigenesis.

Kyritsi K, et al., Abstract 109

# RNA binding protein Apobec1 complementation factor (*A1cf*) regulates multiple hepatic RNAs promoting steatosis, fibrosis, and spontaneous tumorigenesis

## Aims

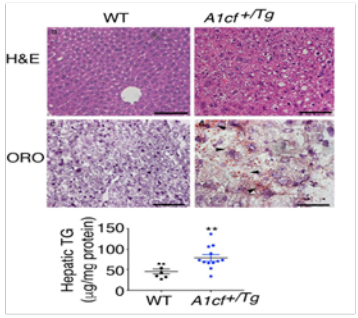
NAFLD may progress to HCC through unknown mechanisms. We examined the role of RNA binding protein *A1cf* as a regulator of APOB and VLDL secretion in promoting HCC.

## Methods

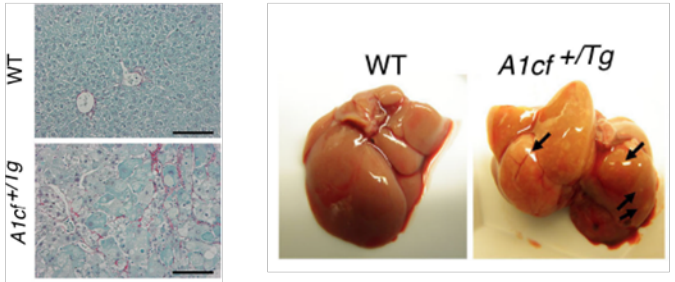
- Hepatocyte-specific *A1cf* transgenic and *A1cf* $^{-/-}$ mice fed chow or high-fat diets and aged for up to 12 months
- RNA-Seq and RNA-CLIP Seq from *A1cf* $^{+/Tg}$ liver
- *A1cf* expression survey in HCC patient cohorts

## Conclusions

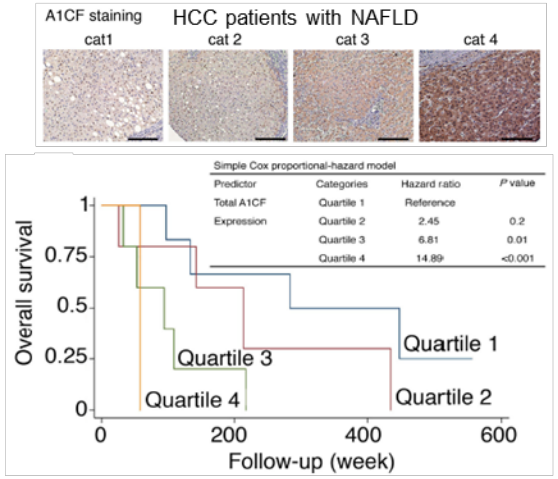
Hepatic *A1cf* overexpression promotes lipogenic, proliferative, and inflammatory pathways leading to HCC in mice, and predicts worse survival in patients with HCC.

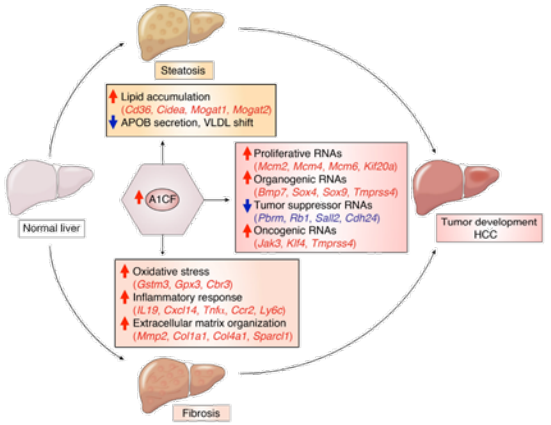


12 weeks steatosis



12 months Fibrosis and tumorigenesis




Blanc V, et al., Abstract 110

# Molecular and mutational landscape of hepatocellular carcinoma (HCC) related to non-alcoholic steatohepatitis (NASH)

## Objective

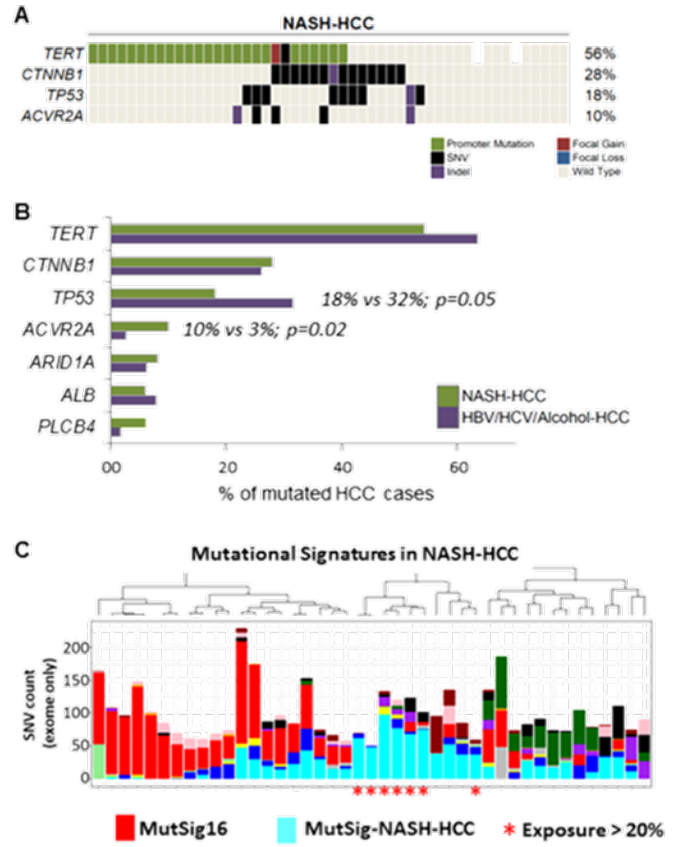
NASH-HCC is molecularly ill-defined. Here, we aimed to identify molecular features that set it apart from other HCC etiologies.

## Methods

Samples from 80 NASH-HCC and 125 NASH patients were collected from 5 institutions, analyzed by expression array and WES, and compared to non-NASH-HCCs. *ACVR2A* function was assessed *in vitro*.

## Main Findings

- *TERT* (56%), *CTNNB1* (28%), *TP53* (18%), and *ACVR2A* (10%) were the most frequently altered genes in NASH-HCC (see Figure A). *ACVR2A* was more mutated in NASH-HCC than in non-NASH-HCC (10% vs 3%, $p<0.05$, see Figure B), and *in vitro* assays suggest it has a potential tumor suppressor role in HCC.
- We identified a novel mutational signature (MutSig-NASH-HCC) enriched in NASH-HCC (16% vs 2% in non-NASH-HCC, $p=0.03$, see Figure C).
- When compared to viral/alcohol-related HCC, NASH-HCCs were enriched in bile and fatty acid signaling, oxidative stress, and inflammation.
- Non-cirrhotic NASH livers were molecularly different from cirrhotic NASH livers. In contrast, in NASH-HCC patients, the cancer field was similar regardless of the patients' cirrhotic status.




## Conclusions

NASH-HCCs display specific molecular features and high prevalence of MutSig-NASH-HCC.

Piqué-Gili M, et al. Abstract 112

# High diagnostic performance of a deep learning artificial intelligence model in accurately diagnosing hepatocellular carcinoma on computed tomography

## Objective

To evaluate an AI model in diagnosing HCC on CT

## Methods

- Thin-cut triphasic liver CT images and clinical information retrieved from six Asian centers.
- HCC diagnosis validated by clinical composite reference standard over subsequent 12 months.
- Deep learning via different classification models

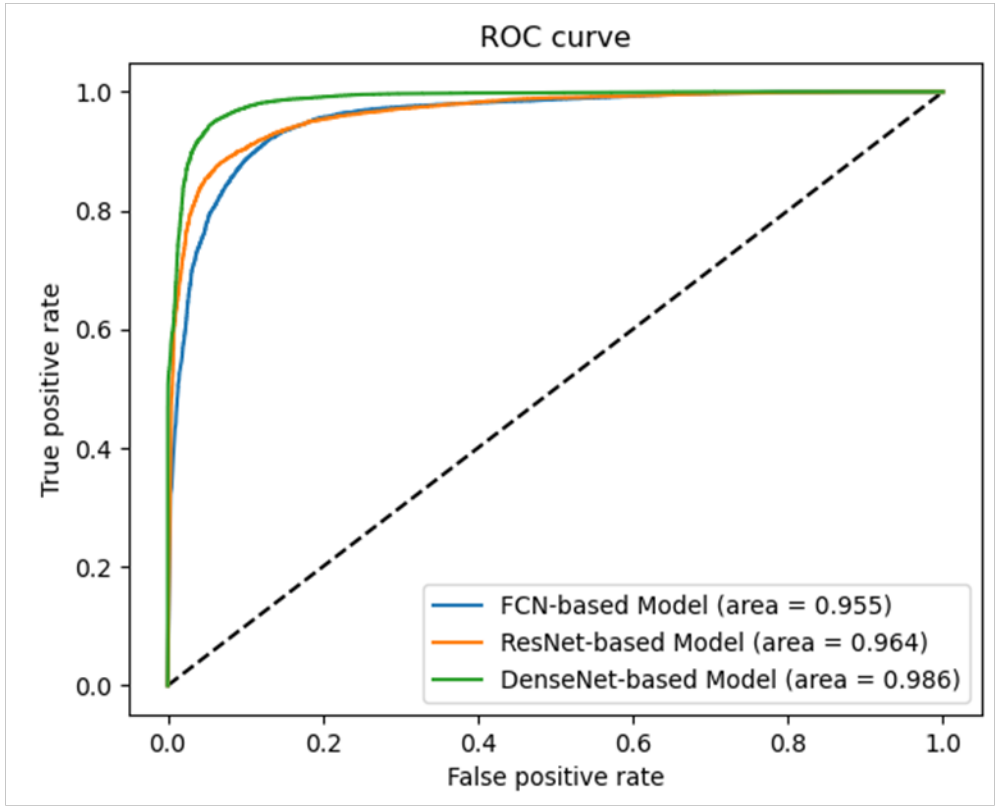
## Main Findings

- High AUROC achieved with DenseNet-based AI model.
- Will undergo external validation

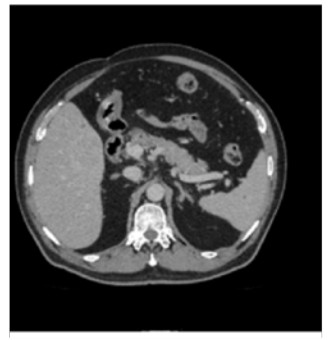
## Conclusions

AI can enhance diagnostic capabilities of CT for HCC.

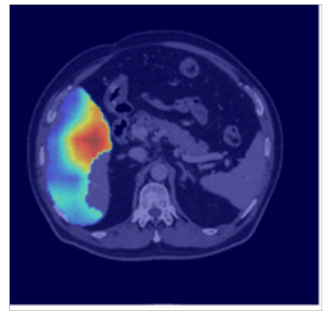
Seto WK, et al., Abstract 114




**N=2551**
(Interim analysis)



**Raw Image (Portovenous)**



**Classification Heat Map**

# Risk of hepatocellular carcinoma in patients with chronic hepatitis C and stage-3 liver fibrosis after sustained virological response (SVR) with direct-acting antivirals (DAA)

## Aim

Study the incidence of hepatocellular carcinoma (HCC) in patients with well-defined baseline stage-3 liver fibrosis after SVR achieved with DAA

## Methods

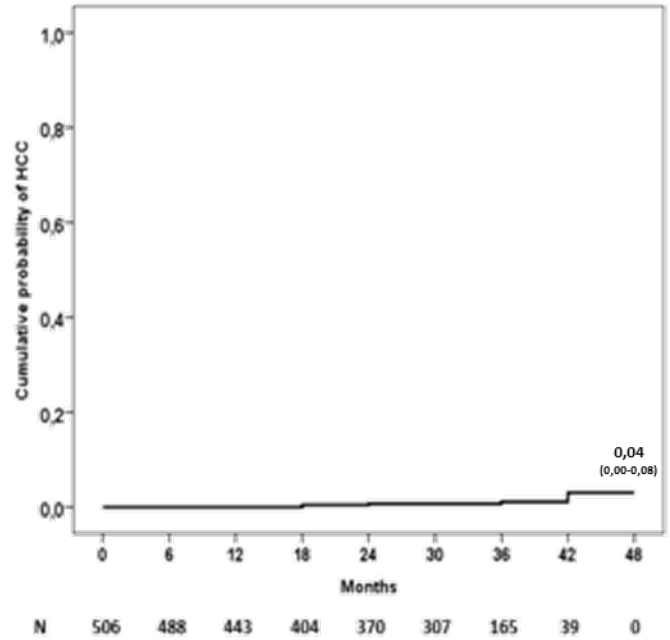
- Multicenter, ambispective, observational study, 12 Spanish hospitals
- Inclusion criteria: Chronic hepatitis C, pre-treatment baseline stage-3 liver fibrosis, and SVR after DAA
  Exclusion criteria: HCC before SVR, concomitant liver disease, cirrhosis, and portal hypertension
- *Baseline stage 3 was defined in a 2-step procedure*: transient elastography values of 9.5-14.5 kPa and subsequently excluded those with nodular liver surface, splenomegaly, ascites, or collaterals on imaging, thrombopenia, or esophago-gastric varices

## Main Findings

- 6 primary liver tumors (PLT). Median follow-up, 33.3 months (21.8-37.3);
  Incidence rate, 0.49 per 100 patient-years (95% CI 0.2-1.01)
- *Male + age >55 and PLT risk*: HR 7.16 ($p$=0.029). Incidence rate 1.10 per 100 patient-years (95% CI 0.30-2.81)

## Conclusions

We found a low incidence of HCC after SVR in a large cohort of well-defined F3 HCV patients assessed using a 2-step stratification process. The only risk factor was being a man >55 years. This risk is below the 1.5% cut-off considered cost-effective for surveillance of HCC.




Cumulative probability of primary liver tumour

Sanchez-Azofra M, et al., Abstract 135

# Striking rural-urban disparities in the incidence of hepatocellular carcinoma in the United States, 1995-2016

## Hypothesis/Aim/Objective

Compare trends in age-adjusted incidence rates of HCC in rural and urban areas of the United States over a 20-year period

## Methods

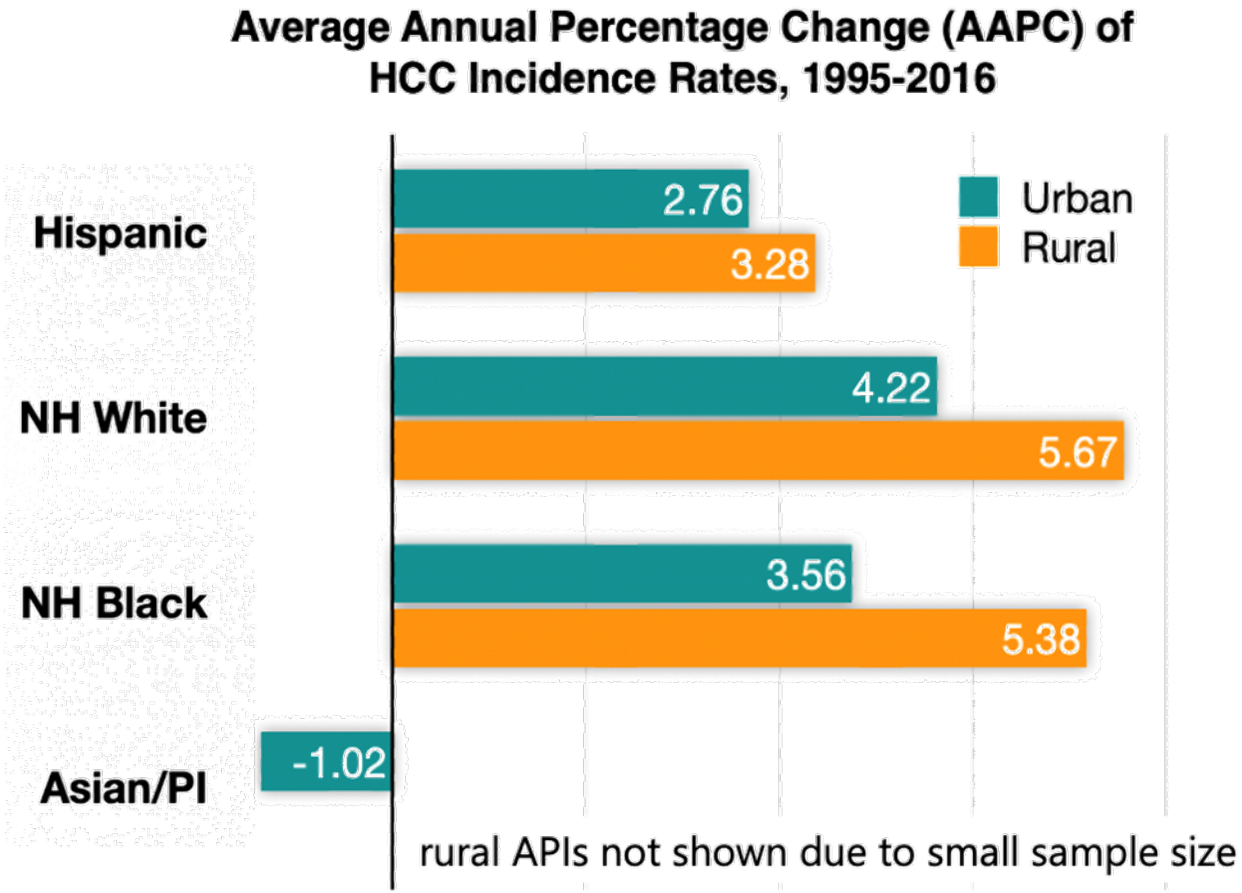
- Analyzed data from NAACCR for HCC incidence 1995-2016
- Joinpoint analysis to evaluate trends

## Main Findings

- Since 2009, the rise in urban incidence has slowed to 2.7% annually.
- In rural areas, incidence continues to rise at a rate of 5.7% per year.

## Conclusions

We identified *striking rural-urban disparities* in HCC incidence trends that vary by *race/ethnicity.*




Gainey CS, et al., Abstract 136

# Association of aspirin and statin use with hepatocellular carcinoma risk in chronic hepatitis B

## Hypothesis/Aim/Objective

To investigate the individual and combined effects of aspirin and statins on HCC risk in antiviral treatment-naïve, non-cirrhotic patients with chronic hepatitis B

## Methods

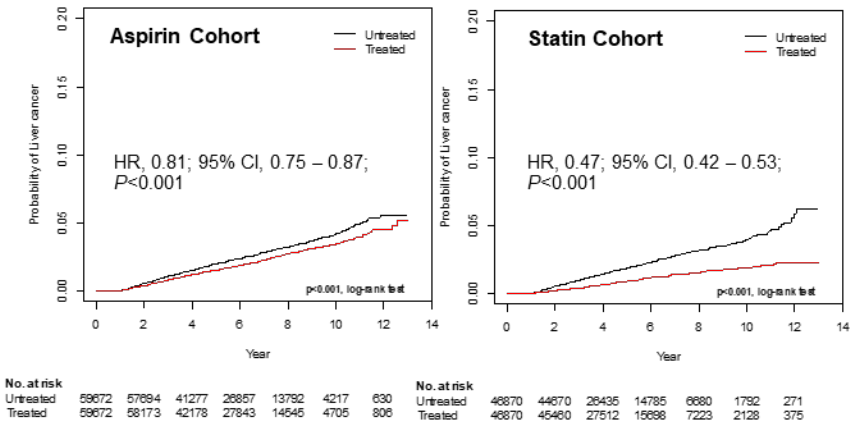
- By using the Korean National Health Insurance Service (NHIS) claims database
- 834,825 antiviral treatment-naïve, non-cirrhotic patients with chronic hepatitis B
- Nationwide population-based nested case-control study
- Separate historical cohort studies with stratified analysis

## Conclusions

- Aspirin and statins were associated with a reduced risk of HCC in antiviral treatment-naïve, non-cirrhotic patients with chronic hepatitis B.
- However, only statin showed consistent and significant dose-dependent reductions in HCC risk.
- Stratified analyses suggested that the benefit of aspirin may have been confounded by statin use.

Choi WM, et al., Abstract 137

| Nested Case-Control Study | Cases (N=15,645) | Controls (N=62,580) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| **Aspirin use – no. (%)** | | | | |
| Never use | 12,643 (80.8) | 47,670 (76.2) | 1.00 (reference) | **1.00 (reference)** |
| Ever use | 3002 (19.2) | 14,910 (23.8) | 0.76 (0.73–0.79) | **0.89 (0.85–0.94)** |
| **Cumulative dose of aspirin use – no. (%)** | | | | |
| Never use | 12,643 (80.8) | 47,670 (76.2) | 1.00 (reference) | 1.00 (reference) |
| T1 (<11 cDDDs) | 460 (2.9) | 2115 (3.4) | 0.82 (0.74–0.91) | 0.85 (0.77–0.95) |
| T2 (11–94 cDDDs) | 1418 (9.1) | 6189 (9.9) | 0.86 (0.81–0.92) | 0.97 (0.91–1.03) |
| T3 (≥94 cDDDs) | 1124 (7.2) | 6606 (10.6) | 0.64 (0.60–0.69) | 0.91 (0.85–0.98) |
| **Statin use – no. (%)** | | | | |
| Never use | 13,310 (85.1) | 44,352 (70.9) | 1.00 (reference) | **1.00 (reference)** |
| Ever use | 2335 (14.9) | 18,228 (29.1) | 0.43 (0.41–0.45) | **0.39 (0.36–0.40)** |
| **Cumulative dose of statin use – no. (%)** | | | | |
| Never use | 13,310 (85.1) | 44,352 (70.9) | 1.00 (reference) | **1.00 (reference)** |
| T1 (<163 cDDDs) | 728 (4.7) | 3811 (6.1) | 0.64 (0.59–0.69) | **0.58 (0.53–0.63)** |
| T2 (163–807 cDDDs) | 1001 (6.3) | 6972 (11.1) | 0.48 (0.45–0.51) | **0.42 (0.39–0.45)** |
| T3 (≥807 cDDDs) | 606 (3.9) | 7445 (11.9) | 0.27 (0.25–0.30) | **0.23 (0.21–0.26)** |




| Stratified Analysis in Aspirin Historical Cohort | | |
|---|---|---|
| **Aspirin** | **Statin** | **HR (95% CI)** |
| Untreated | Treated vs Untreated (ref) | **0.31 (0.29–0.33)** |
| Treated | Treated vs Untreated (ref) | **0.38 (0.33–0.44)** |

| Stratified Analysis in Statin Historical Cohort | | |
|---|---|---|
| **Statin** | **Aspirin** | **HR (95% CI)** |
| Untreated | Treated vs Untreated (ref) | **1.00 (0.94–1.06)** |
| Treated | Treated vs Untreated (ref) | **0.98 (0.78–1.22)** |

# Outcomes of transplantation for HBV- vs HCV-related HCC: impact of DAA HCV therapy in a national analysis of >18,000 patients

## Aim

Compare post-transplant (LT) outcomes for HBV-HCC vs HCV-HCC according to DAA era in a large national study

## Methods

- A total of 30,886 HCC-related LTs were performed from 2003-2013.
- Patients were grouped based on therapy: pre-DAA (January 2003-October 2013) and post-DAA (November 2013-January 2019) eras.
- Outcomes for patients with HBV (n=2141) vs HCV (n=16,574) were compared in each DAA.
- Logistic regression was used to identify predictors of post-LT survival.

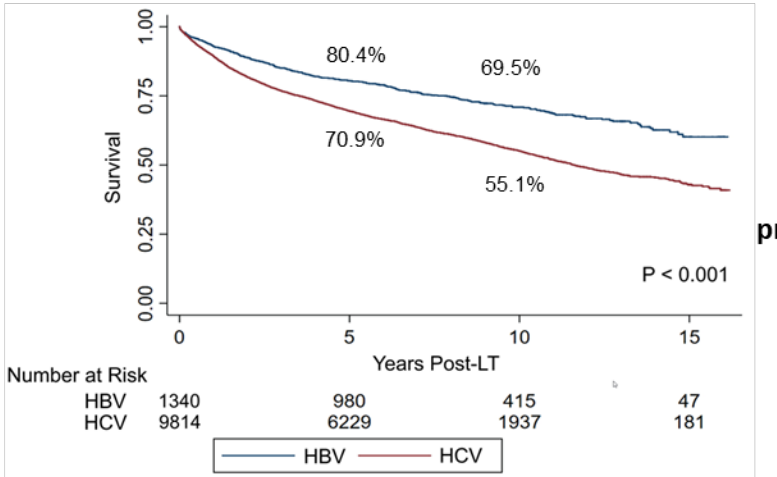
## Results

Independent predictors of lower post-LT survival included higher MELD score ($p$<0.001), pre-LT AFP level >20 ng/mL ($p$<0.001), outside Milan status at diagnosis ($p$=0.03), vascular invasion ($p$<0.001), and mod/poor tumor differentiation ($p$<0.001). HCV status did not predict outcome in the post-DAA era after adjusting for tumor characteristics.

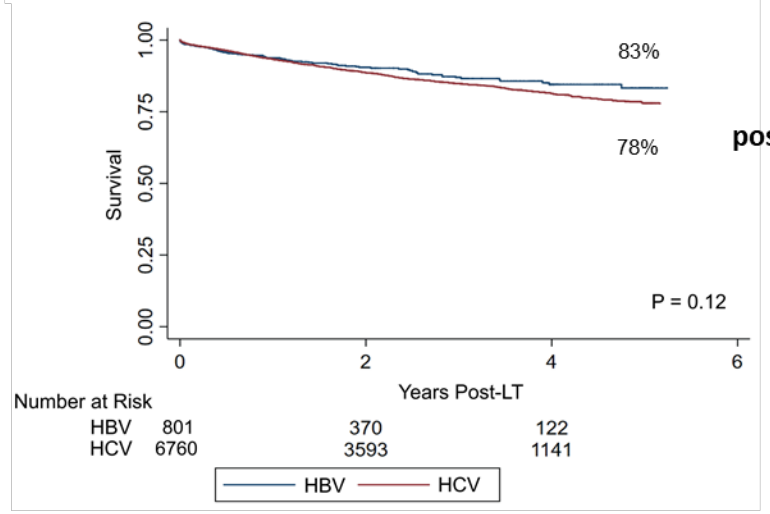
## Conclusion

This large national study demonstrates that after the introduction of effective DAA HCV therapy, results of LT for HCV-HCC are significantly improved and are no longer statistically different from results in patients with HBV-HCC.

Tabrizian P, et al., Abstract 138




pre-DAA era




post-DAA era

# Carvedilol and risk of hepatocellular carcinoma in the United States: a retrospective analysis

## Hypothesis/Aim/Objective

This study determines the risk of hepatocellular carcinoma (HCC) among cirrhotic patients with carvedilol treatment.

## Methods

- This retrospective cohort study utilized the Cerner Health Facts database in the United States from 2000 to 2017.
- Patients aged 18 or older who were diagnosed with cirrhosis were included.
- Propensity score matching and multivariate logistic regression were used to test the risk of HCC among the carvedilol group compared with propranolol, nadolol, and no beta-blocker group.

## Conclusions

Carvedilol was associated with a significantly decreased risk of HCC in patients with cirrhosis when compared with propranolol, nadolol, or no beta-blocker.

Wijarnpreecha K, et al., Abstract 1037

| Disease Groups | Medication | Before Matching | | After Matching | |
|---|---|---|---|---|---|
| | | Multivariate analysis OR (95% CI) | *P* value | Multivariate analysis OR (95% CI) | *P* value |
| Cirrhosis (n= 124,361) | no beta-blockers (n=95,943) | Reference | | Reference | |
| | Carvedilol (n=11,574) | 0.37 (0.32 - 0.43) | <0.001* | 0.40 (0.34 - 0.47) | <0.001* |
| | Propranolol (n=11,100) | 0.90 (0.81 - 0.99) | 0.030* | 0.89 (0.79 - 0.99) | 0.041 * |
| | Nadolol (n=5744) | 0.91 (0.80 - 1.04) | 0.166 | 0.88 (0.75 - 1.03) | 0.111 |
| Cirrhosis with Complications (n=68,346) | no beta-blockers (n=47,172) | Reference | | | |
| | Carvedilol (n=6254) | 0.32 (0.27 - 0.38) | <0.001* | 0.33 (0.27 -0.40) | <0.001* |
| | Propranolol (n=9682) | 0.63 (0.57 - 0.70) | <0.001* | 0.64 (0.57 - 0.71) | <0.001* |
| | Nadolol (n=5238) | 0.60 (0.53 - 0.69) | <0.001* | 0.60 (0.52 - 0.70) | <0.001* |

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