Hepatocellular Carcinoma

Abstracts from AASLD 2018

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HCC Abstracts, AASLD 2018

- Changing epidemiology
- Prevention
- Who should we be screening
- How should we be screening
- New data in surgical therapy: resection and transplant
- New data in locoregional therapy
- Systemic treatment

HCC Abstracts, AASLD 2018

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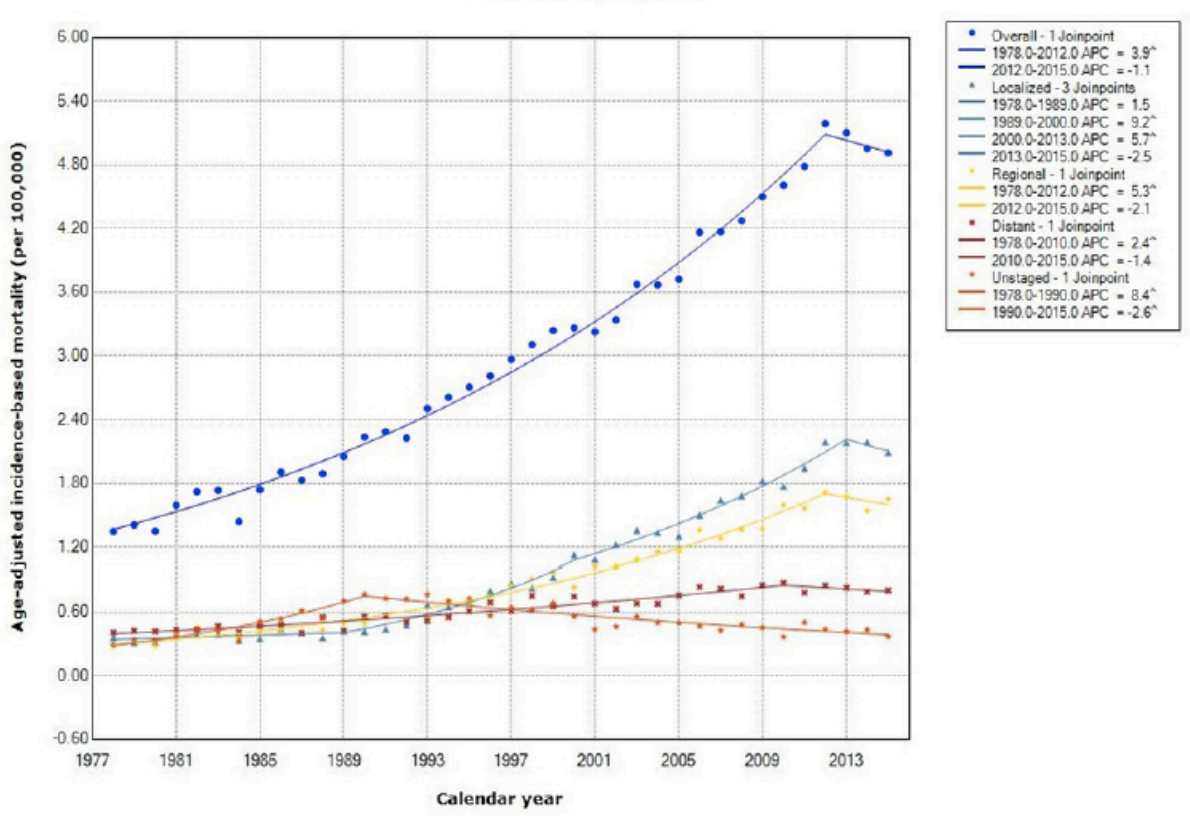
Trends in Hepatocellular Carcinoma Incidence, Mortality, and Survival in the United States, 1974-2015

Dr. Parag Mahale and Eric A Engels, Division of Cancer Epidemiology and Genetics, National Cancer Institute



- HCC incidence increasing from 1974 through 2013
- From 2013-2015, HCC incidence and incidence based mortality stabilized for all stages of disease
- 5 year survival rates increased from 3.7% in 1974 to 21.2% in 2010, mostly due to increased survival in localized stage (9.8% to 35.1%

In Medicare Patients with HCC, NAFLD is Among the Top Causes for Mortality and Resource Utilization

Figure 1. HCC rate from Medicare population by etiology, stratified by race

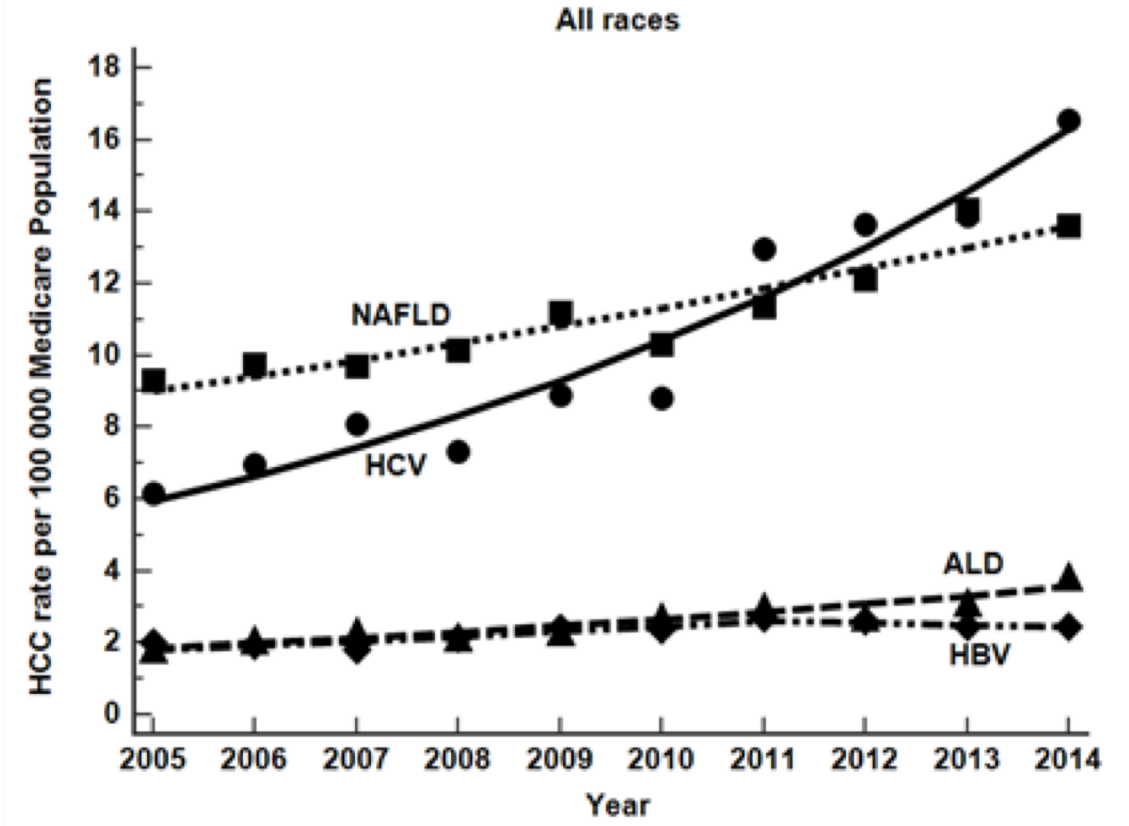
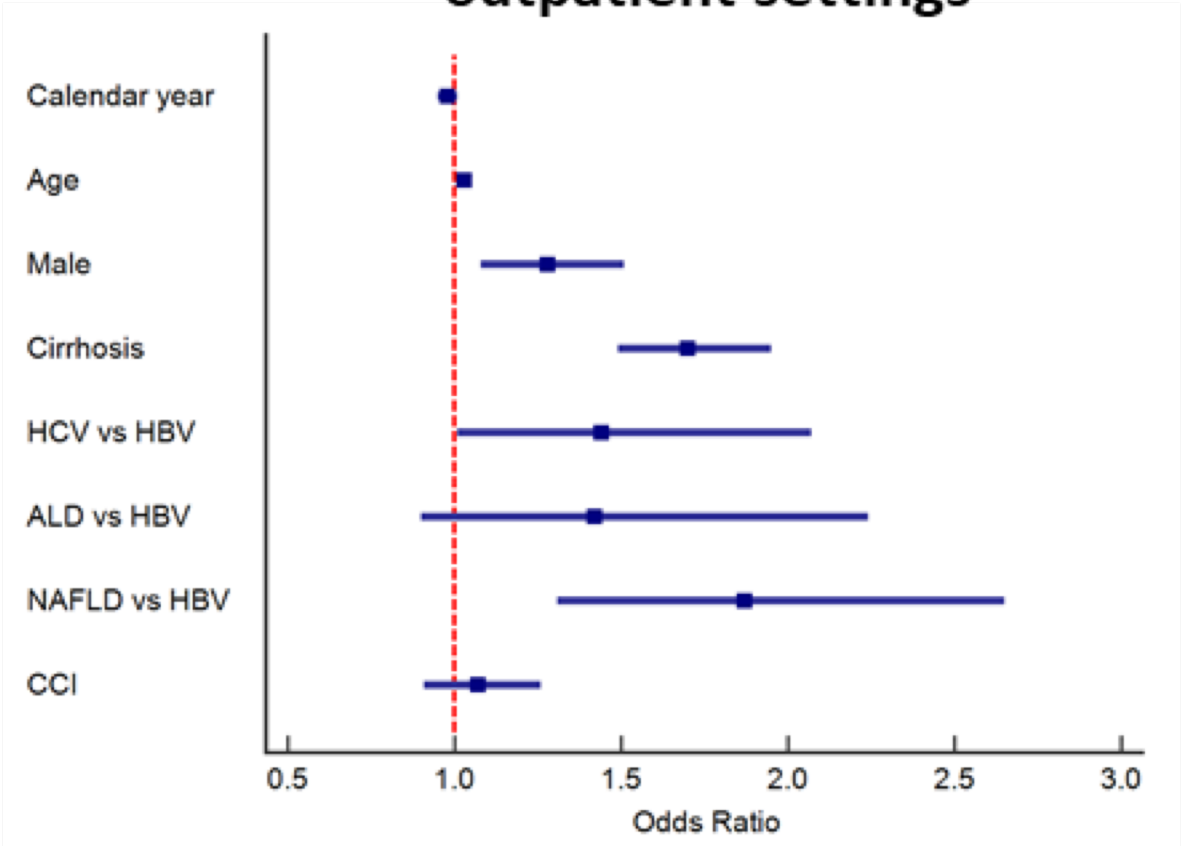


Figure 2. Predictors of 1-year mortality in outpatient settings



Shahab et al, Abstract 273

HCC Abstracts, AASLD 2018

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Thiazolidinediones Reduce the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B and Diabetes Mellitus - a Cohort Study of 29,221 Subjects

Mr. Cheuk Fung Yip[1], Prof. Grace Lai[2], Mr. Yee-Kit Tse[1], Dr. Henry Lik Yuen Chan[2] and Prof. Vincent Wai Sun Wong[2], (1)Institute of Digestive Disease, and Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, (2)Institute of Digestive Disease, Department of Medicine and Therapeutics, and State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong

- Patients with chronic hepatitis B and diabetes from 2000-2017
- 29,221 patients identified
- 2,701 developed HCC (9.3%) after median follow up 7.2 years
- Anti-diabetic agents and other medications reviewed for all patients

Abstract 2079

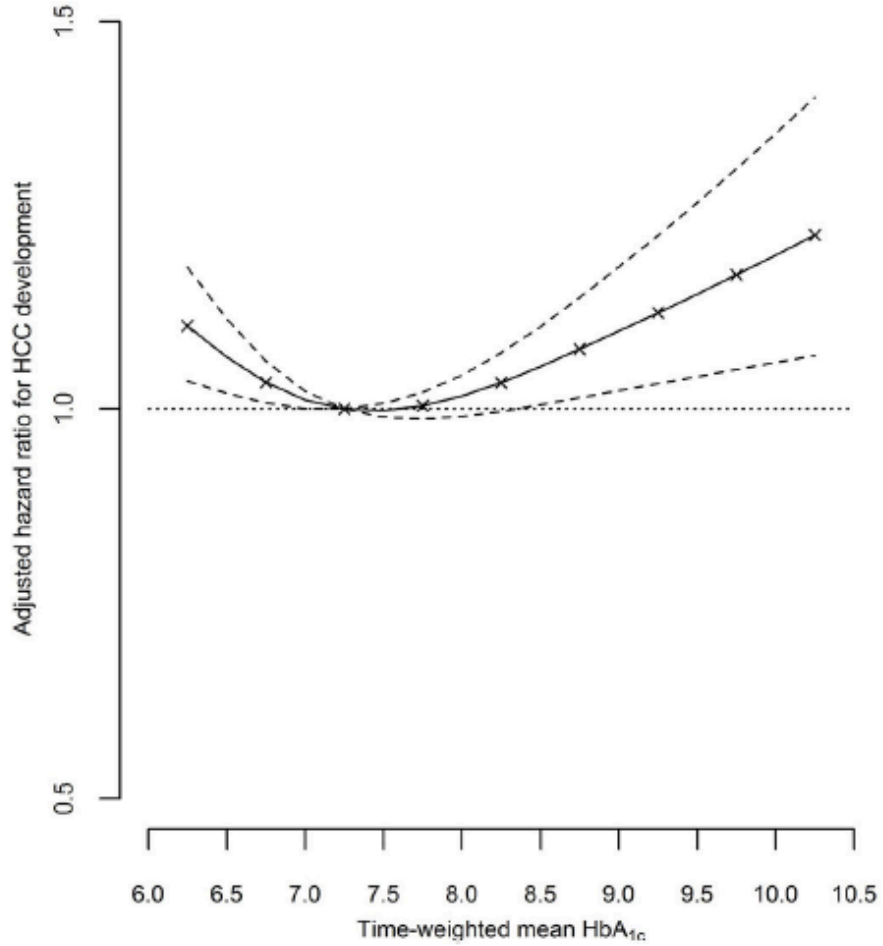
Thiazolidinediones Reduce the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B and Diabetes Mellitus - a Cohort Study of 29,221 Subjects

Mr. Cheuk Fung Yip[1], Prof. Grace Lai[2], Mr. Yee-Kit Tse[1], Dr. Henry Lik Yuen Chan[2] and Prof. Vincent Wai Sun Wong[2], (1)Institute of Digestive Disease, and Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, (2)Institute of Digestive Disease, Department of Medicine and Therapeutics, and State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong

Parameters	Univariate Analysis			Multivariable Analysis (N=27,434)*		
	Hazard ratio	95% CI	*P* values	Adjusted hazard ratio	95% CI	*P* values
Use of thiazolidinedione	0.27	0.13 – 0.57	<0.001	0.47	0.22 – 0.98	0.045
Use of metformin	0.50	0.46 – 0.55	<0.001	0.74	0.68 – 0.81	<0.001
Use of sulfonylureas	1.03	0.95 – 1.11	0.459	1.11	1.01 – 1.21	0.023
Use of insulin	1.89	1.72 – 2.07	<0.001	1.53	1.38 – 1.70	<0.001
Use of alpha glucosidase inhibitor	1.19	0.85 – 1.65	0.308			
Use of DPP-4 inhibitors	0.93	0.75 – 1.16	0.514			
Use of SGLT2 inhibitors	0.61	0.15 – 2.43	0.482			
Use of statins	0.57	0.52 – 0.63	<0.001	0.83	0.75 – 0.93	<0.001
Use of aspirin or clopidogrel	0.87	0.79 – 0.97	0.009	0.79	0.71 – 0.88	<0.001
Use of ACEI or ARB	0.87	0.80 – 0.94	<0.001			

Glycemic Control and HCC Risk

- Same patient population evaluated for affect of glycemic control on HCC development



Fung-Yip et al, Abstract 2110

The association between aspirin use and risk of hepatocellular carcinoma (HCC)

Aim:

To examine the potential benefits of aspirin use for primary HCC prevention at a range of doses and durations of use, within two prospective, nationwide populations

Methods:

- Pooled, prospective cohort study of 133,371 adult men and women in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), with validated biennial medication use data since 1980 (NHS) and 1986 (HPFS).
- Cox proportional hazards regression models were used to calculate multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for incident HCC.

Simon et al, Abstract 91

The association between aspirin use and risk of hepatocellular carcinoma (HCC)

Figure 1A. Duration of Aspirin Use[1] and Risk of Hepatocellular Carcinoma risk

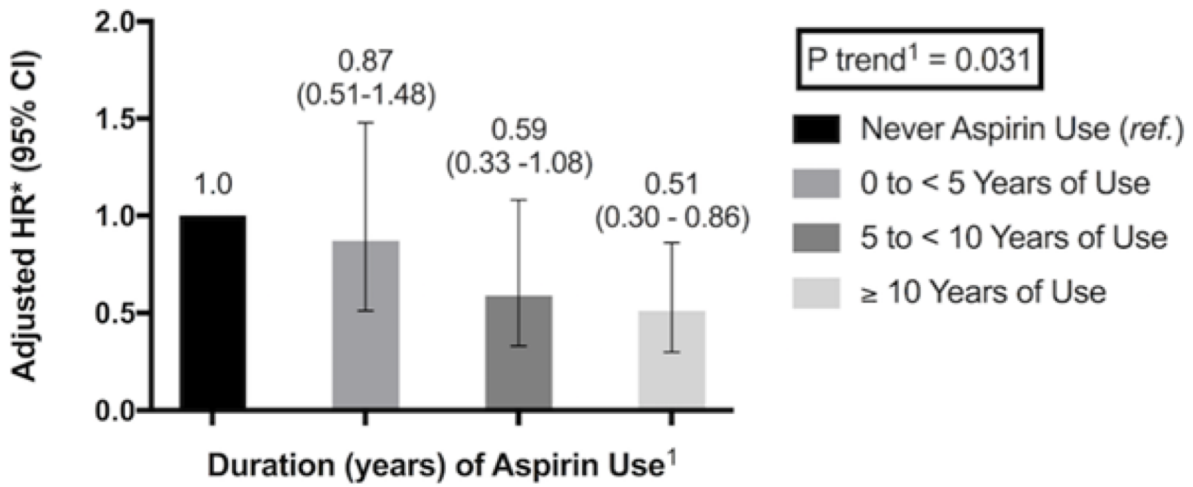
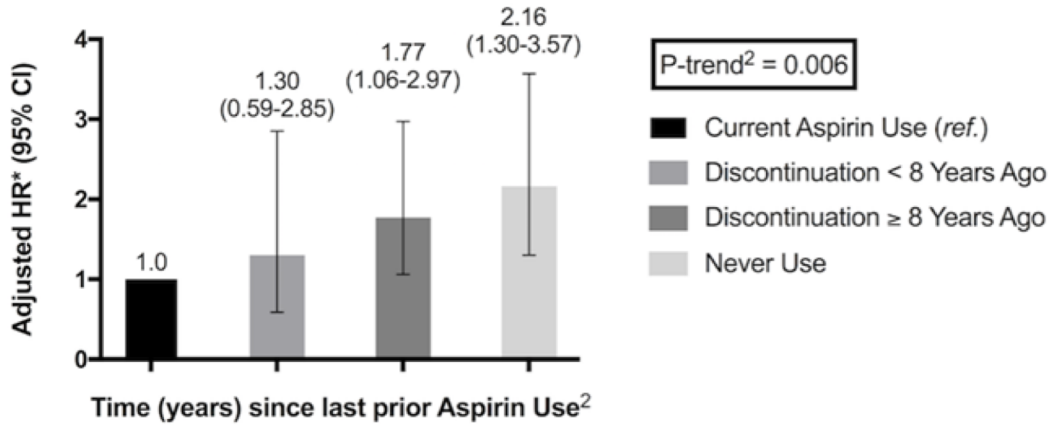


Figure 1B. Time Since Discontinuation of Aspirin[2] and Hepatocellular Carcinoma Risk



* Model conditioned on age (years), sex/cohort, race/ethnicity, type 2 diabetes, hypertension, hyperlipidemia, statin use, metformin use, and non-aspirin nonsteroidal anti-inflammatory drug (NSAID) use, with all covariates updated over time.

Simon et al, Abstract 91

Lipophilic statins and risk of hepatocellular carcinoma (HCC) and mortality in chronic viral hepatitis

Aim:

To examine the associations between lipophilic and hydrophilic statin use and risk for incident HCC and death, in a prospective, nationwide population with confirmed chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection

Methods:

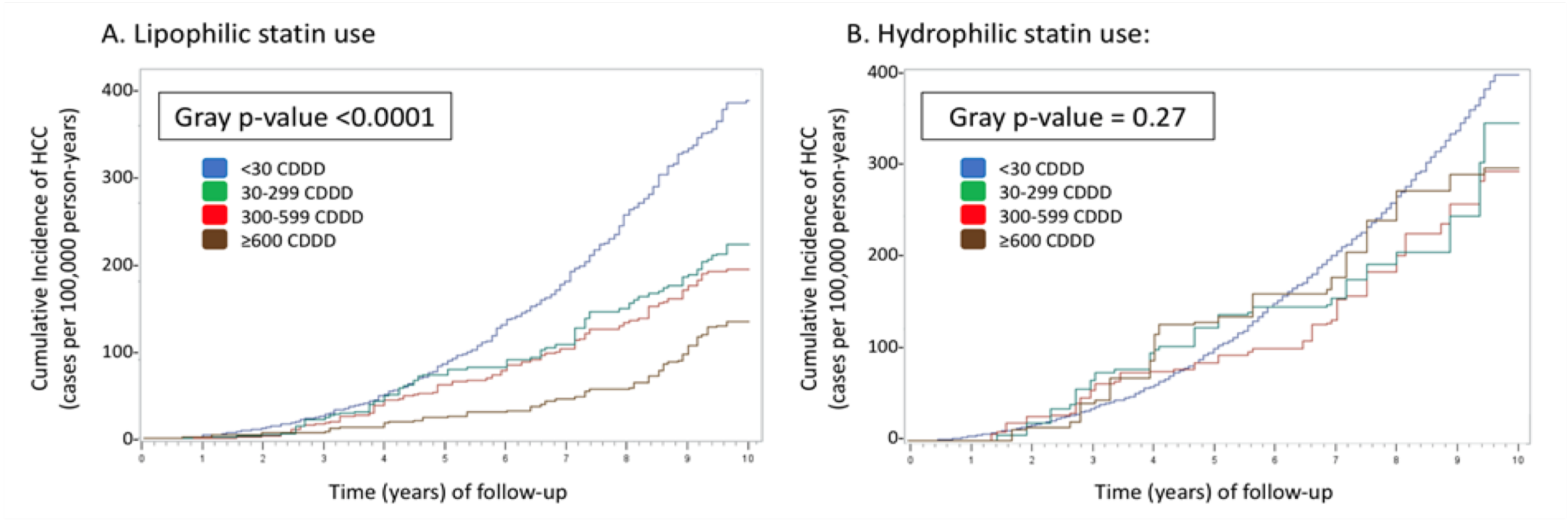
- Using validated Swedish nationwide registers, we conducted a prospective, nationwide cohort study, using a 1:1 propensity score-matched, new-user design.
- Using Cox proportional hazards modeling that accounted for competing risks, we estimated the subdistribution hazard ratios and 95% confidence intervals for incident HCC and death.

Simon et al, Abstract 93

Lipophilic statins: Atorvastatin, lovastatin, simvastatin
Hydrophilic statins: pravastatin, rosuvastatin, fluvastatin

Lipophilic statins and risk of hepatocellular carcinoma (HCC) and mortality in chronic viral hepatitis

Cumulative incidence of HCC with lipophilic statins (A) or hydrophilic statins (B)



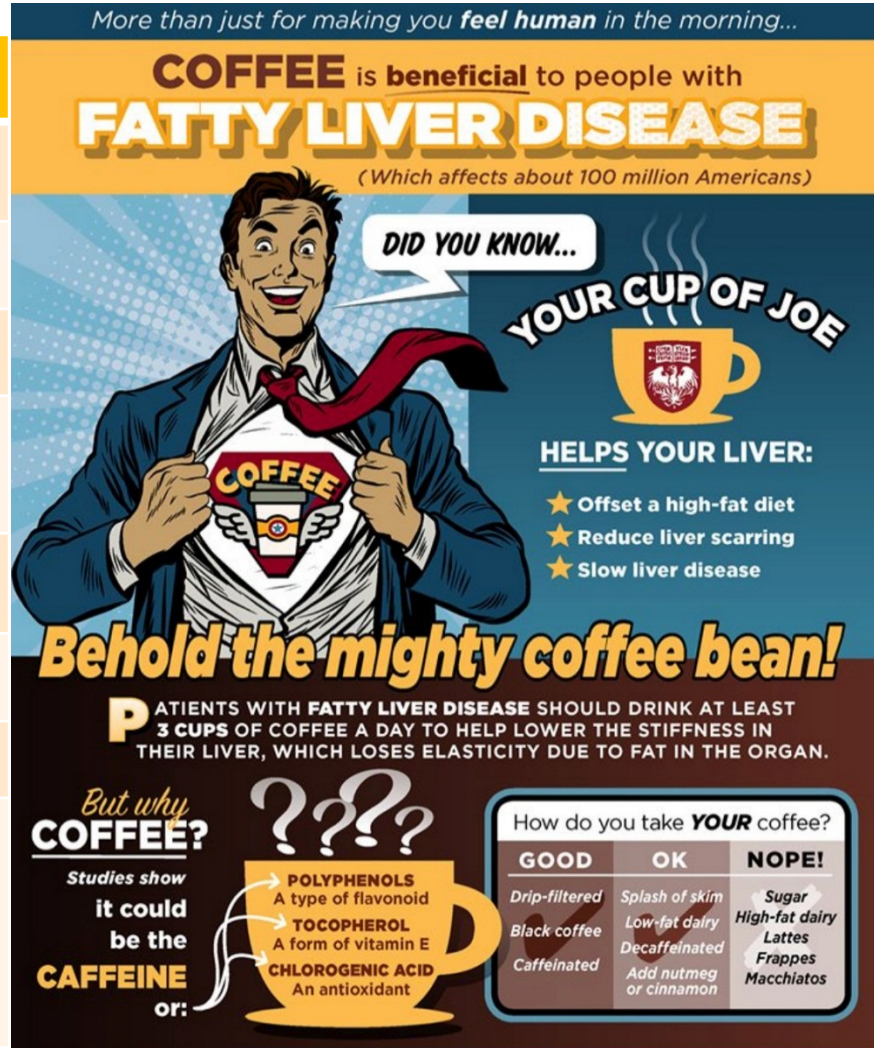
cDDD, cumulative defined daily dose

Lipophilic statins: Atorvastatin, lovastatin, simvastatin
Hydrophilic statins: pravastatin, rosuvastatin, fluvastatin

Simon et al, Abstract 93

Behold The Mighty Coffee Bean!

Authors	N	Dose	Findings
Klatsky 1992	128,934	>4 cups/d	1/5 the risk of alcoholic cirrhosis
Ruhl 2005	9849	>2 cups/d	½ the risk of chronic liver disease
Bravi 2007	1551	2 cups/d	43% lower risk of HCC
Freedman 2009	766	>3 cups/d	53% decreased progression of HCV
Johnson 2011	63,257	>3 cups/d	45% lower risk of HCC
Molloy 2012	306	2 cups/d	Lower risk of fibrosis in NASH
Matsuura 2012	3285	>4 cups/d	Lower risk of metabolic syndrome
Setiawan 2015	>215,000	>2 cups/d >4 cups/d	38% less HCC, 46% less chronic liver disease 41% less HCC, 71% less chronic liver disease



- In patients with chronic hepatitis, antiviral therapies leading to maintained HBV suppression in chronic hepatitis B and sustained viral response in hepatitis C are recommended, since they have been shown to prevent progression to cirrhosis and HCC development (**evidence high; recommendation strong**).
- Once cirrhosis is established, antiviral therapy is beneficial in preventing cirrhosis progression and decompensation. Furthermore, successful antiviral therapy reduces but does not eliminate the risk of HCC development (**evidence moderate**). Antiviral therapies should follow the EASL guidelines for management of chronic hepatitis B and C infection.
- Patients with HCV-associated cirrhosis and HCC treated with curative intent, maintain a high rate of HCC recurrence even after subsequent DAA therapy resulting in sustained viral response. It is presently unclear whether this represents the inherent risk of HCC development in advanced cirrhosis, or if DAA therapy increases recurrence rates. Thus, further research is encouraged. Currently, close surveillance is advised in these patients. The benefit of viral cure must be weighed against a potentially higher recurrence risk (**evidence low; recommendation strong**).
- Coffee consumption has been shown to decrease the risk of HCC in patients with chronic liver disease. In these patients, coffee consumption should be encouraged (**evidence moderate; recommendation strong**).

New EASL HCC Clinical Practice Guidelines: 2018

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Prediction and need for HCC surveillance after first 5 years of ETV/TDF therapy in Caucasian CHB patients of PAGE-B cohort

Hypothesis/Aim/Objective:

To assess predictors and need for HCC surveillance beyond year 5 of ETV/TDF in CHB patients

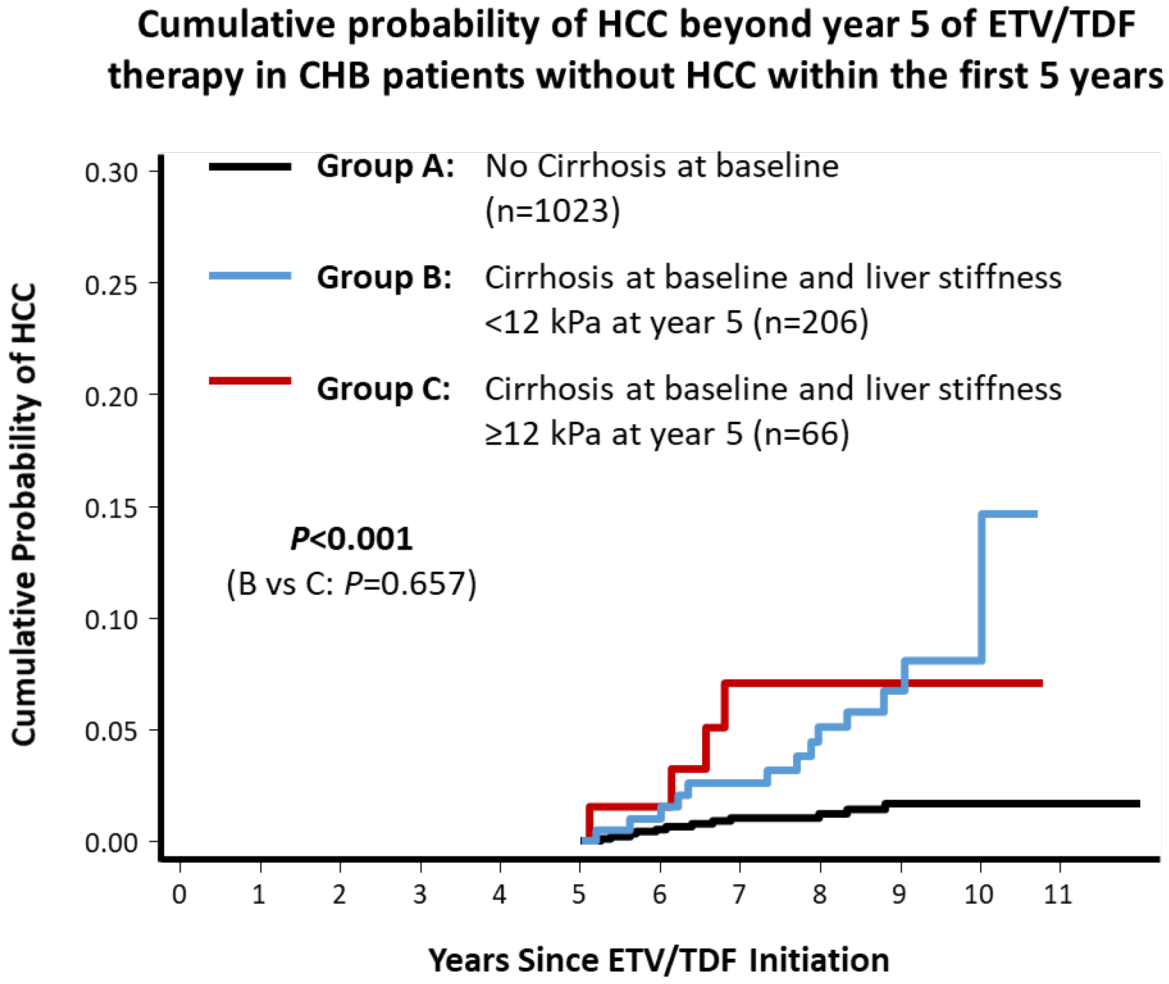
Methods:

- Patient population: 1427 (73%) of the 1951 adult Caucasians with CHB ± compensated cirrhosis included in the PAGE-B cohort who have completed follow-up >5 years without HCC until year 5
- Age at year 5: 57 ± 13 years, males: 70%, baseline cirrhosis: 26%
- Mean follow-up: 8.1 ± 1.6 (median: 8.3) years from ETV/TDF onset

Papatheodoridis et al, Abstract 17

ETV, entecavir; TDF, tenofovir disoproxil

Prediction and need for HCC surveillance after first 5 years of ETV/TDF therapy in Caucasian CHB patients of PAGE-B cohort



- HCC in chronic HBV patients after 5 years of therapy with ETV/TDF occurred exclusively in patients over the age of 50
- Reversal of cirrhosis by elastography did not decrease the risk of HCC development

Papatheodoridis et al, Abstract 17

ETV, entecavir; TDF, tenofovir disoproxil

ALT levels and HCC risk in Caucasian CHB patients under long-term therapy with ETV or TDF

Hypothesis/Aim/Objective:

To assess whether ALT levels affect the incidence of HCC in CHB patients treated with long-term ETV/TDF therapy

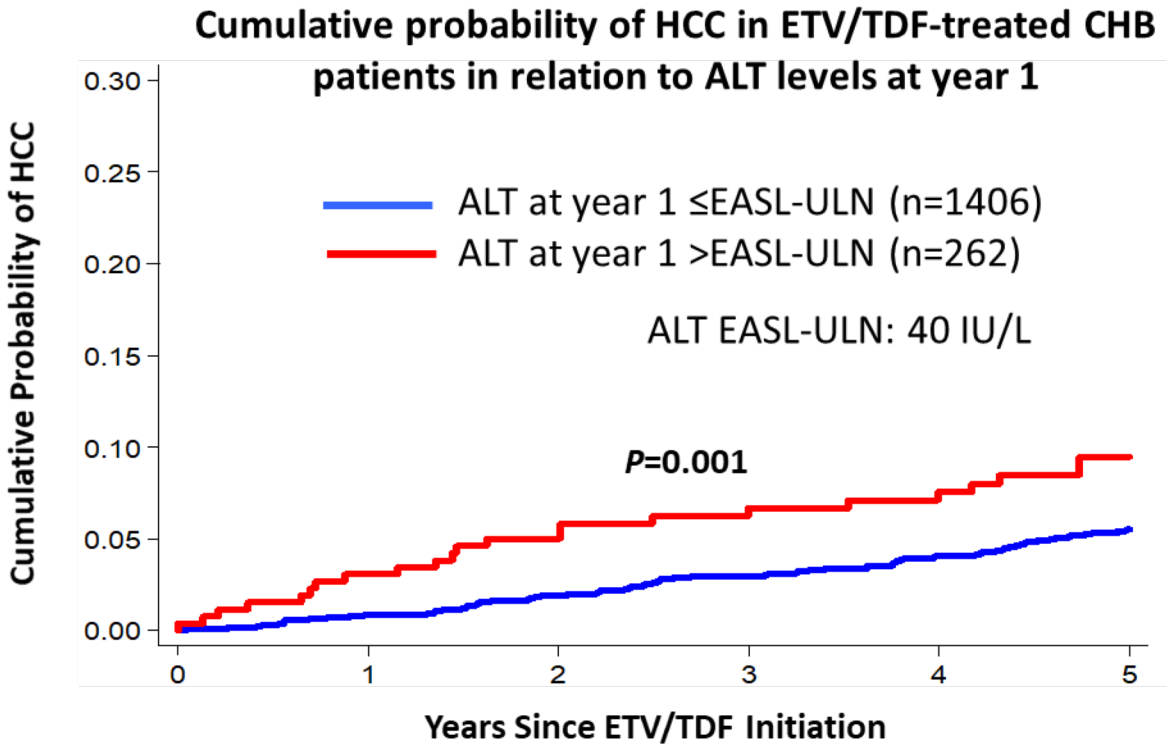
Methods:

- PAGE-B cohort: 1951 adult Caucasians with CHB ± compensated cirrhosis
- Age: 53 ± 14 years, males: 71%, HBeAg-positive: 18%, compensated cirrhosis: 27%
- Mean follow-up: 6.9 ± 2.8 (median: 7.3) years from ETV/TDF onset

Papatheodoridis et al, Abstract 265

ETV, entecavir; TDF, tenofovir disoproxil

ALT levels and HCC risk in Caucasian CHB patients under long-term therapy with ETV or TDF



ALT >EASL-ULN at year 1 was independently associated with development of HCC in patients with baseline cirrhosis (adjusted HR: 2.9, 95% CI: 1.3-3.9; *P*=0.003)

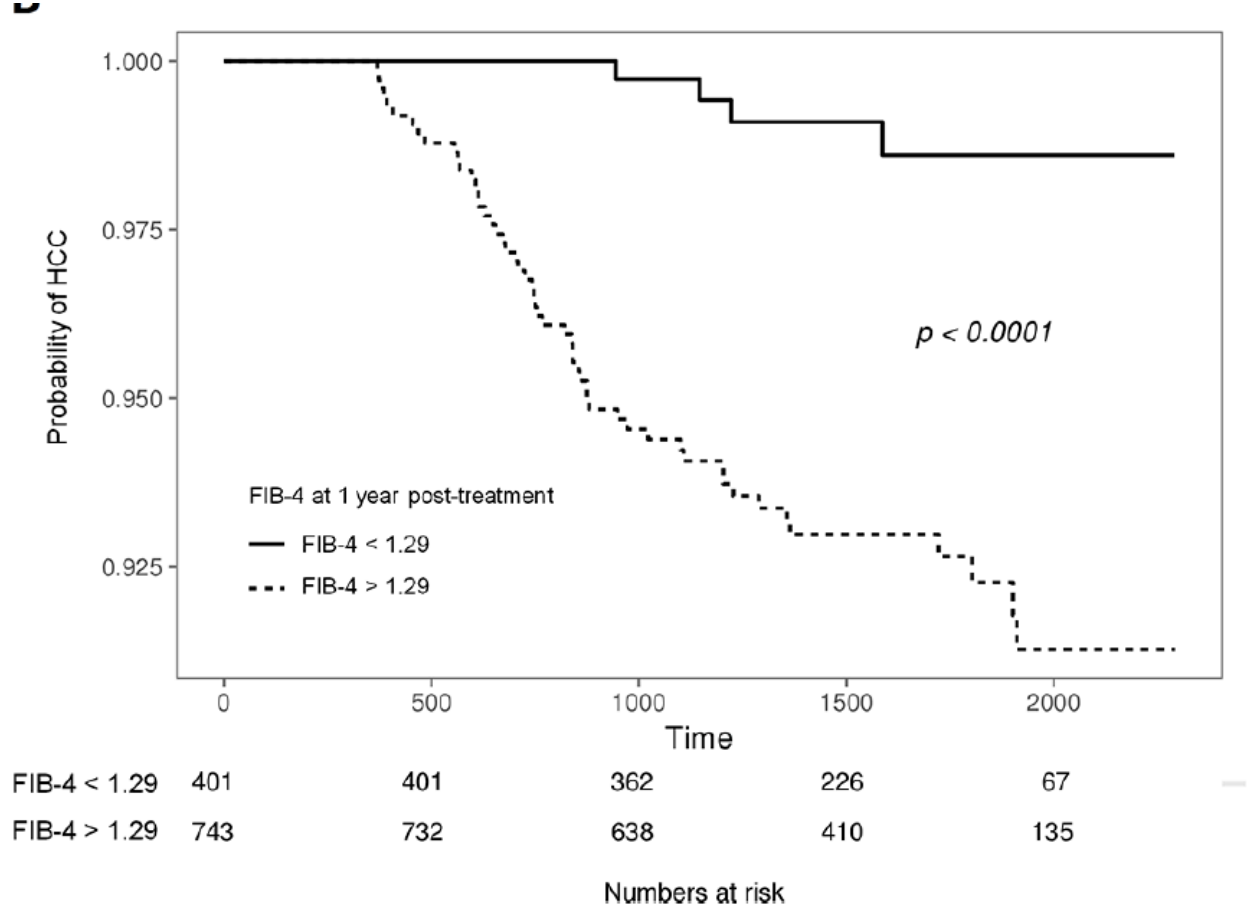
- In patients on therapy for chronic hepatitis B with entecavir or tenofovir, elevated ALT at one year of therapy increased the risk of HCC development
- This effect was particularly seen in patients with cirrhosis at baseline

Papatheodoridis et al, Abstract 265

ETV, entecavir; TDF, tenofovir disoproxil

FIB-4 at One Year of Therapy for HBV Can Also be Used to Predict HCC Risk

$$FIB4 = [age\ x\ AST]/[Plt\ x\ \sqrt{ALT}]$$



Woo Oh et al, Abstract 2095

Differences in Hepatocellular Carcinoma Risk, Predictors and Trends over Time According to Etiology of Cirrhosis: A Cohort of 116,404 Patients with Cirrhosis Including 10,042 Who Developed HCC.

Dr. George Ioannou[1,2], Dr. Pamela Green[3], Dr. Elliott Lowy[3], Dr. Elijah Mun[2] and Dr. Kristin Berry[3], (1)Medicine, Veterans Affairs Puget Sound Healthcare System, (2)Medicine, University of Washington, (3)Research and Development, Veterans Affairs Puget Sound Healthcare System

- 116,404 VA patients with cirrhosis diagnosed between 2001-2014
- 10,042 new HCC cases seen in median follow up of 4.2 years
- HCV had >3x higher risk of HCC than ALD, NAFLD, or other causes
- HCC incidence was 1.6x higher in cirrhosis dx'd 2007-2014 compared to 2001-2007
- Independent risk factors for HCC development were age, male sex, Hispanic ethnicity, AFP elevation, alkaline phosphatase elevation, AST/ALT ratio, low serum albumin, platelet count
- Diabetes increased HCC development in ALD and NAFLD cirrhosis

Abstract 274

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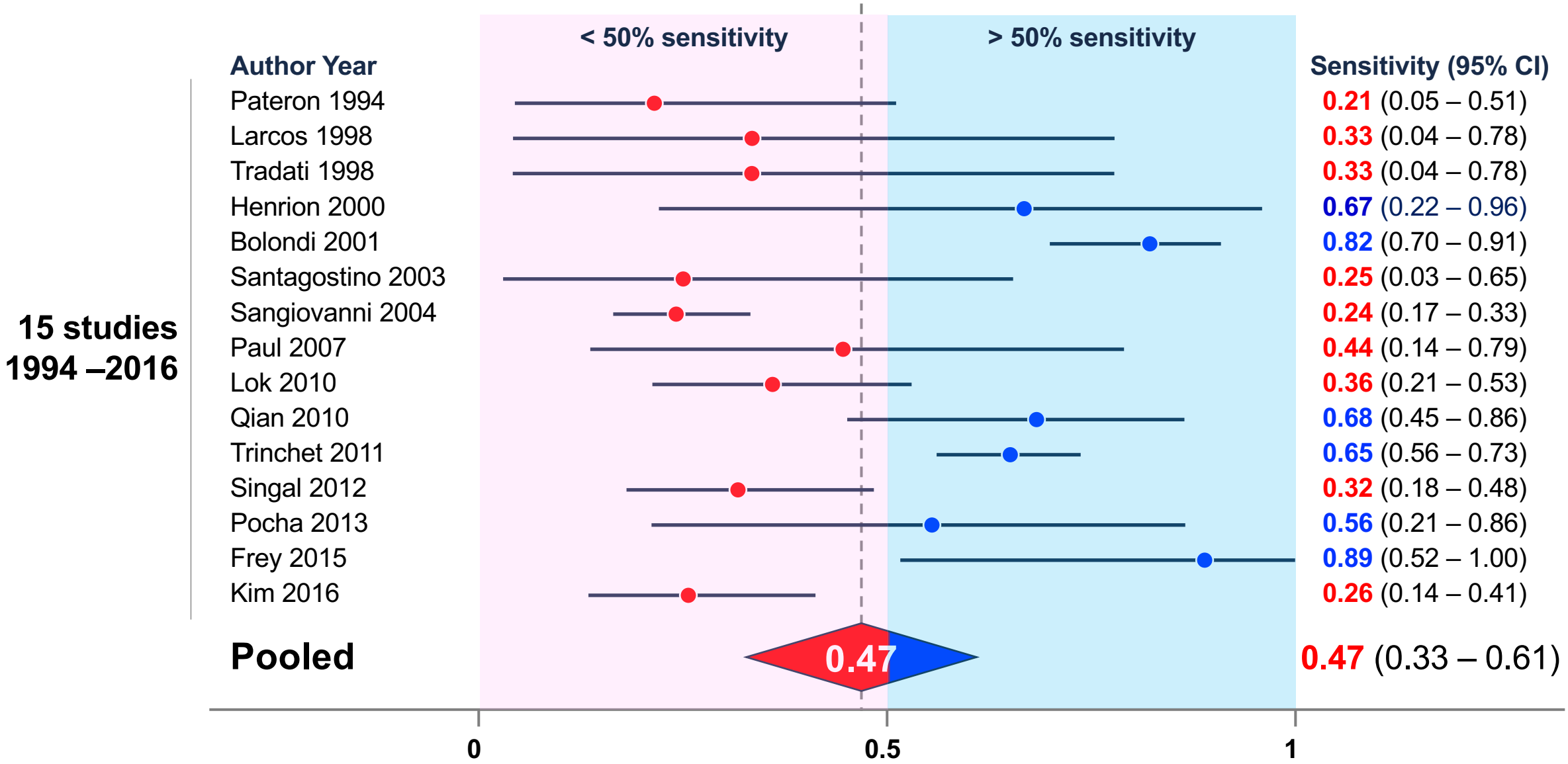
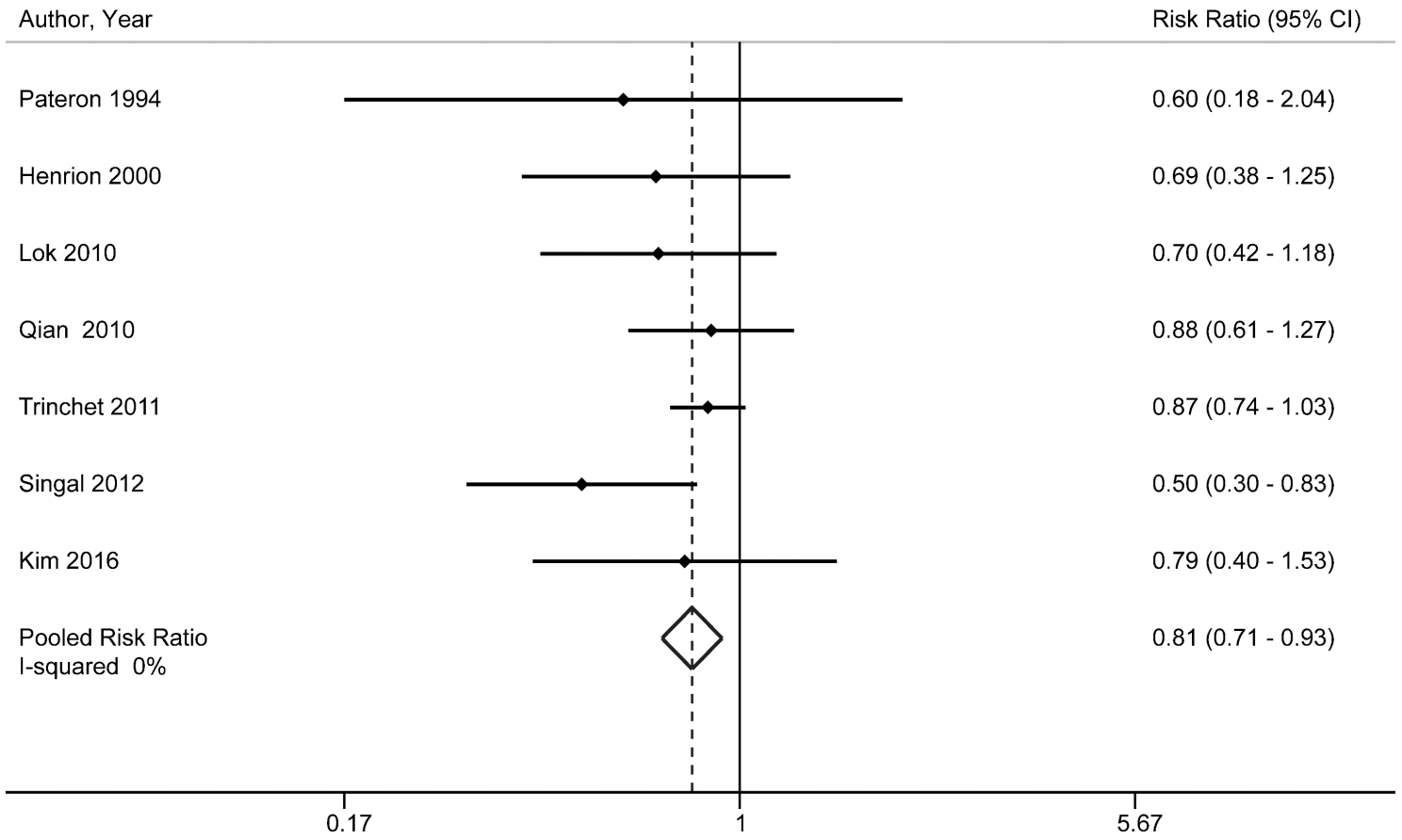
Meta-Analysis: Sensitivity of Ultrasound Alone for Early HCC



Singal, ILCA 2018

Meta-Analysis: Sensitivity of Ultrasound +/- AFP for Early HCC



Sensitivity ultrasound 45% (30-62%) vs. US+AFP: 63% (48-75%)

Benefit of AFP consistent across subgroups

Prospective studies:
RR 0.78 (0.66 – 0.92)
Studies in United States:
RR 0.59 (0.41 – 0.85)
Cirrhosis-only studies:
RR 0.76 (0.60 – 0.95)
Studies after 2000:
RR 0.79 (0.66 – 0.95)

Singal, ILCA 2018

Alternate Dynamic Computed Tomography and Ultrasonography for Surveillance of Chronic Hepatitis B Patients with Cirrhosis at High Risk of Hepatocellular Carcinoma

Dr. Minjong Lee[1], Dr. Ji Hyun Kim[2], Prof. Seonghee Kang[3], Dr. Baek Gyu Jun[4], Dr. Tae Suk Kim[1], Prof. Ki Tae Suk[5], Dr. Moon Young Kim[3], Dr. Young Don Kim[4], Dr. Gab Jin Cheon[4], Dong Joon Kim[5], Dr. Soon Koo Baik[3] and Dr. Dae Hee Choi[1], (1)Department of Internal Medicine, Kangwon National University Hospital, (2)Baengnyeong-Ro 156, Chuncheon-Si, Gangwon-Do Kangwon National University Hospital 200-722, Baengnyeong-Ro 156, Chuncheon-Si, Gangwon-Do Kangwon National University Hospital 200-722, (3)Department of Internal Medicine, Wonju Severance Christian Hospital, (4)Department of Internal Medicine, Gangneung Asan Hospital, (5)Department of Internal Medicine, Hallym University College of Medicine

- 636 HBV patients under entecavir/tenofovir therapy retrospectively reviewed
- HCC detection rates compared for US every 6 months vs alternate dynamic contrast CT and US every 6 months
- 5 year cumulative HCC rates 13.7% in total population
- Alternating CT and US resulted in improved detection while BCLC stage 0 or A (p=0.007, p=0.02), HR 2.52 (95% CI 1.41-4.51, p=0.002)

Magnetic Resonance Imaging Is Cost-Effective for Hepatocellular Carcinoma Surveillance in High Risk Patients with Cirrhosis

Prof. Hye-Lin Kim[1], Prof. Jihyun An[2], Ms. Jae-A Park[3], Mr. Seung-Hoo Park[3], Prof. Eui-Kyung Lee[3] and Prof. Young-Suk Lim[4], (1)College of Pharmacy, Sahmyook University, (2)Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Songpa, Seoul, Korea (the Republic of), (3)School of Pharmacy, Sungkyunkwan University, (4)Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea (the Republic of)

- Markov model developed to compare expected costs and quality adjusted life-years of HCC surveillance with semi-annual MRI with liver-specific contrast agent vs semi-annual ultrasound
- Use of MRI incurred $3,439 incremental costs, 0.546 incremental life-years, and 0.315 incremental QALY
- Incremental cost-effectiveness ratio for MRI was below the cost effective threshold of $50,000 QALY when annual HCC incidence was >1.89% per year
- ICER was $10,991/QALY for MRI when HCC incidence >5%/year

Abstract 998

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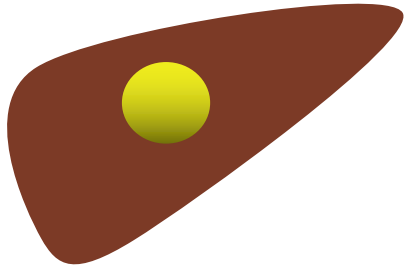
Transient Elastography May Be Helpful Prior to Resection or Transplant for HCC

- Abstract 1129: 267 HCC patients who underwent resection had Lsby shear wave velocity before surgery
  - Liver stiffness was the only independent risk factor for post operative ascites ($p<0.01$)
  - Cut off to predict post operative ascites 1.79 m/s (equivalent to F3/F4)
- Abstract 1517: 208 patients before resection or OLT had LS and CAP scores prior to surgery
  - LS >30 poor prognostic indictor for overall survival with resection (HR 3.46)
  - LS >30 in OLT candidates was independent risk factor for dropout
  - LS >30 (HR 5.33) and CAP score <240 (HR 9.46) in patients with F3/F4 were predictors for early recurrence of HCC

Abstracts 1129 and 1517

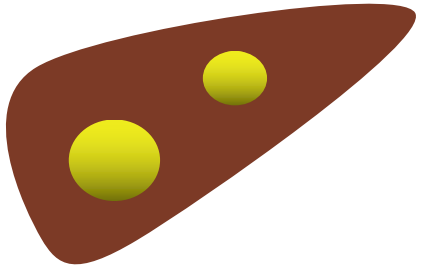
LS, liver stiffness; CAP, controlled attenuation parameter; OLT, orthotopic liver transplant

National experience on down-staging of HCC before liver Tx: Influence of tumor burden, AFP, and wait time



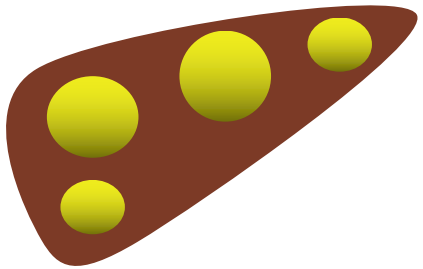
MILAN

- 1 lesion ≤ 5 cm
- Up to 3 lesions ≤ 3 cm
- No extra-hepatic disease or vascular invasion



"UNOS-DS"

- 1 lesion 5.1-8 cm
- 2 or 3 lesions ≤ 5 cm
- 4 or 5 lesions ≤ 3 cm
- Total diameter ≤ 8 cm
- No extra-hepatic disease or vascular invasion



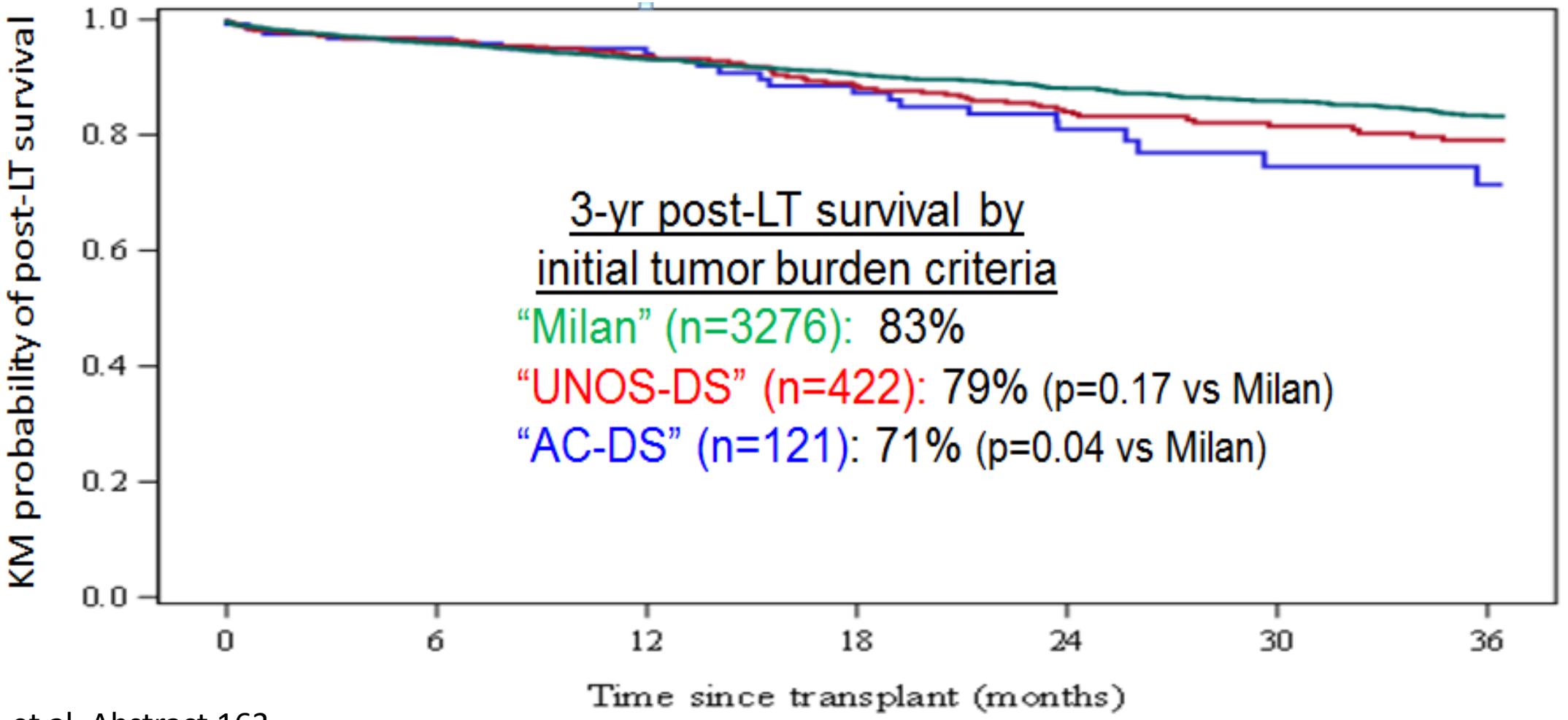
"AC-DS"

- Tumor size, number or total tumor diameter beyond "UNOS-DS"
- No extra-hepatic disease or vascular invasion

Mehta et al, Abstract 163

POST-TRANSPLANT SURVIVAL

- Median post-LT f/u 1.9 years (1.0-2.4)

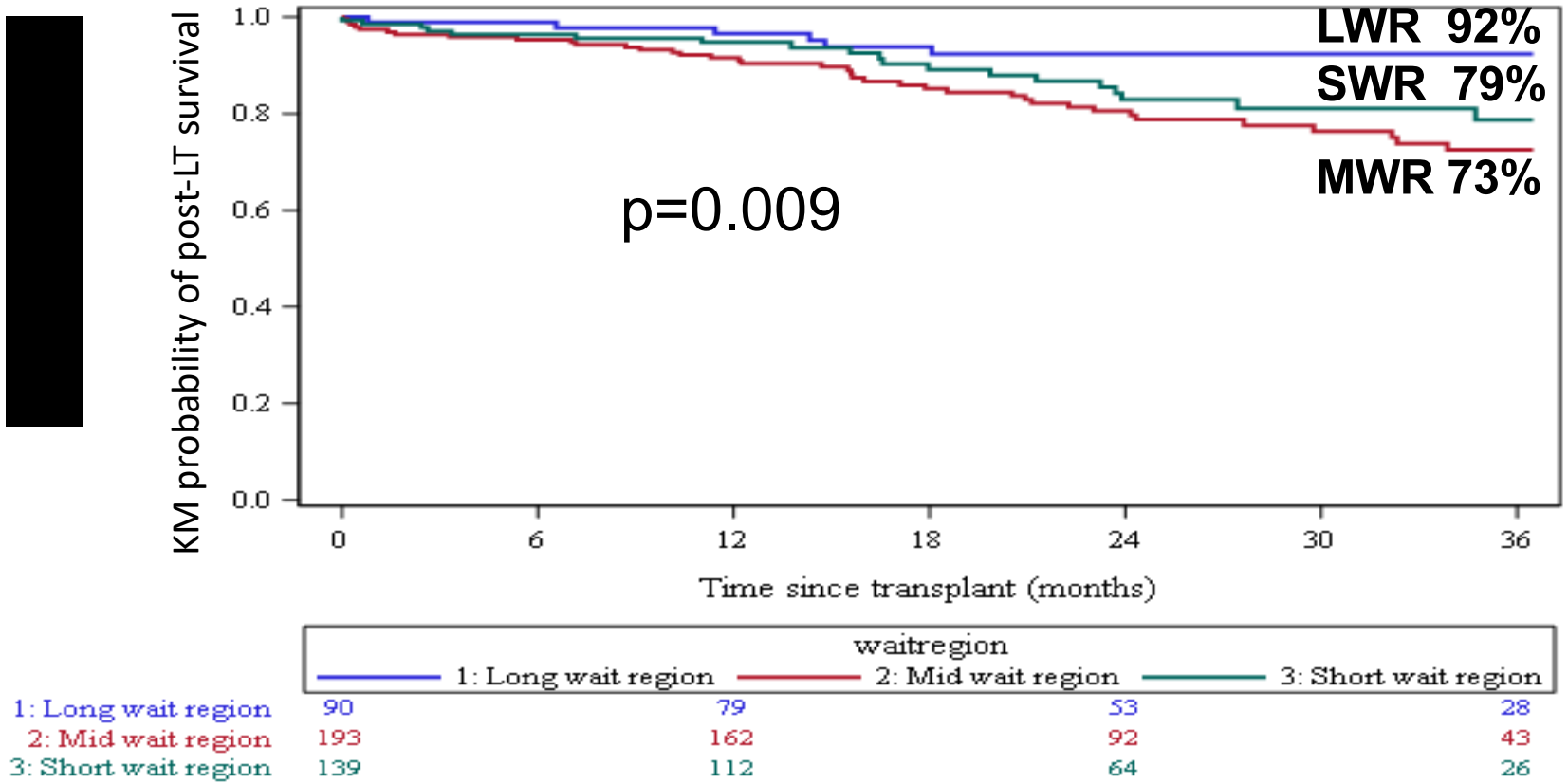


Mehta et al, Abstract 163

POST-LT SURVIVAL BY TUMOR BURDEN CRITERIA AND WAIT REGION

- "Milan": No post-LT survival differences by wait region

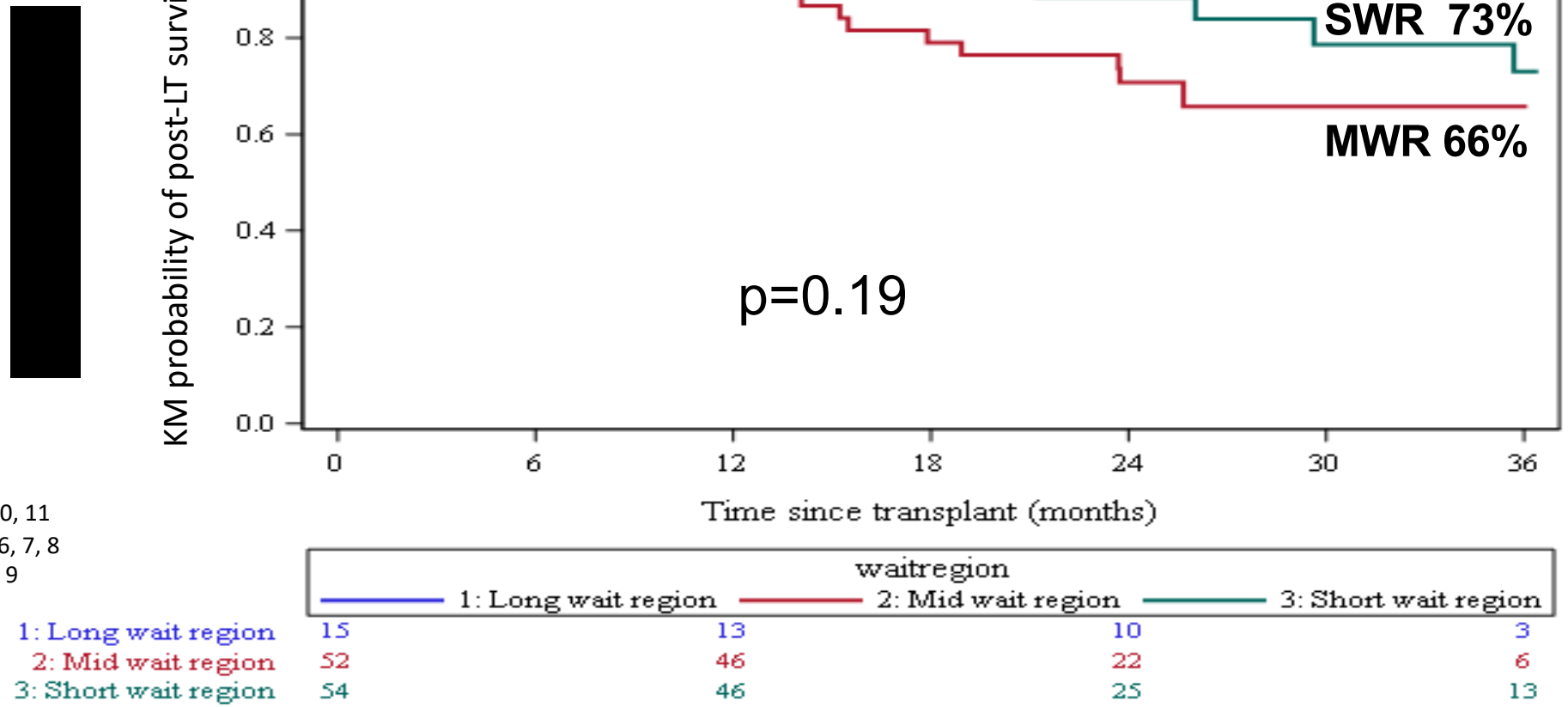
- "UNOS-DS": Survival differences by wait region (n=422)



Short wait time regions: 3, 10, 11
Mid wait time regions: 2, 4, 6, 7, 8
Long wait time regions: 1, 5, 9

POST-LT SURVIVAL BY TUMOR BURDEN CRITERIA AND WAIT REGION

- "AC-DS" (n=121)



Short wait time regions: 3, 10, 11
Mid wait time regions: 2, 4, 6, 7, 8
Long wait time regions: 1, 5, 9

Mehta et al, Abstract 163

PRE-LT PREDICTORS OF POST-LT DEATH AMONG PTS EVER BEYOND MILAN (n=543): MULTI-VARIABLE ANALYSIS

Predictor	UV HR (95% CI)	p-value
AFP ≥100 ng/ml (vs <20)	2.4 (1.2-4.5)	0.009
AFP 20-99 ng/ml (vs <20)	1.4 (0.9-2.4)	0.15
Mid and Short Wait Region (vs Long)	3.1 (1.4-6.7)	0.005

Short wait time regions: 3, 10, 11
Mid wait time regions: 2, 4, 6, 7, 8
Long wait time regions: 1, 5, 9

Mehta et al, Abstract 163

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Reason of Discontinuation after Transarterial Chemoembolization Influences Survival in Patients with Hepatocellular Carcinoma

Mr. Tim Labeur, Cancer Center Amsterdam; Gastroenterology & Hepatology, Academic Medical Center, Dr. Bart Takkenberg, Gastroenterology and Hepatology, AMC, Dr. Heinz-Josef Klümpen, Medical Oncology, Academic Medical Center and Prof. Otto Van Delden, Radiology, Academic Medical Center

- 192 patients received a median of 2 TACEs (range 1-7)
- Reasons for discontinuation of TACE
  - Tumor progression in 74%
  - Liver dysfunction (CP>B7) in 19%
- Patients who discontinued due to liver dysfunction only 8% recovered well enough to receive second line therapy
- Patients who were able to receive second line therapy had overall survival of 21 months vs 12 months in others ($p<0.001$)

Abstract 1471

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AASLD THE LIVER MEETING® 2018 SAN FRANCISCO NOVEMBER 9-13

Nivolumab in Patients With Child-Pugh B Advanced Hepatocellular Carcinoma in the CheckMate 040 Study

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Key Eligibility Criteria

Key Inclusion Criteria
Histologically confirmed advanced HCC not eligible for surgical and/or locoregional therapy
≥ 1 untreated lesion measurable by RECIST v1.1
HBV-HCC, HCV-HCC, or non–viral-related HCC
No prior sorafenib treatment, or documented radiographic progression on or intolerance to sorafenib
Child-Pugh score of B7 or B8
No ascites (1 point) or mild ascites (2 points)
Eastern Cooperative Oncology Group performance status of 0 or 1
Key Exclusion Criteria
Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
Active brain metastases or leptomeningeal metastases
Active co-infection with both HBV and HCV
History of hepatic encephalopathy within 6 months of screening
History of hepatorenal syndrome
Paracentesis for treatment of ascites within 3 months of screening
Prior liver transplant

HBV, hepatitis B virus; HCV, hepatitis C virus.

Best Overall Response

Investigator Assessment

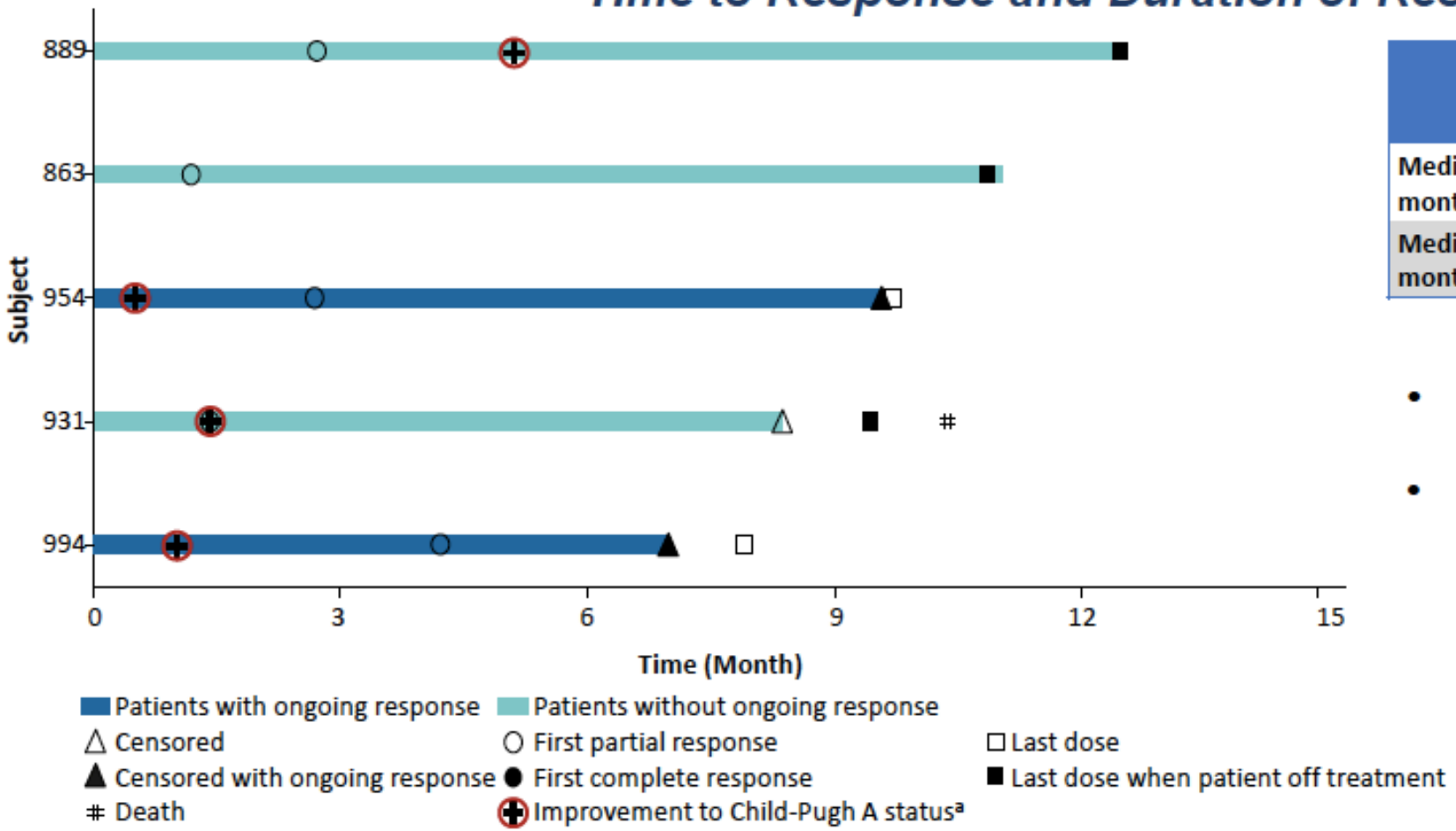
	Child-Pugh B	Child-Pugh A[a,b]
	All Subjects N = 49	Cohorts 1 & 2 N = 262
Objective response using RECIST v1.1, n (%)	5 (10.2)	53 (20.2)
Best overall response		
Complete response	0	8 (3.1)
Partial response	5 (10.2)	45 (17.2)
Stable disease	22 (44.9)	107 (40.8)
Progressive disease	15 (30.6)	88 (33.6)
Unable to determine	7 (14.3)	14 (5.3)
Disease control rate, n (%)	27 (55.1)	160 (61.1)

- ORR and disease control rate by investigator assessment were 10% and 55%, respectively

[a]Data from CheckMate 040 cohorts 1 and 2, in which almost all patients had Child-Pugh A status, are presented for comparison.
[b]In cohorts 1 & 2, best overall response was not reported for 2 patients.

Characterization of Response

Time to Response and Duration of Response



	Child-Pugh B	Child-Pugh A
	All Subjects N = 49	Cohorts 1 & 2 N = 262
Median time to response, months (range)	2.7 (1.2–4.2)	2.7 (1.2–16.4)
Median duration of response, months (range)	9.9 (2.8+–9.9)	12.4 (2.8–51.1+)

- At the time of data cutoff 2 patients had ongoing response
- **4 of 5 responders improved from Child-Pugh B status at baseline to Child-Pugh A5 or A6 status for at least 6 months**

CR, complete response; PR, partial response.

[a]Improvement to Child-Pugh A status represents the first time point at which patient improved from Child-Pugh B to Child-Pugh A status and maintained for ≥6 months.

Conclusions

- HCC incidence and mortality stabilizing for the first time in 40 years
- NAFLD is an increasing cause and cost of care in HCC
- TZDs, glycemic control, aspirin, lipophilic statins, and coffee may decrease the risk of HCC
- Chronic HBV patients
  - If on therapy >5 years, risk of HCC seen in patients over the age of 50, and reversal of cirrhosis on elastography does NOT protect against HCC development
  - If ALT is still elevated at one year, risk of HCC is increased
  - FIB-4 can be used to predict increased risk of HCC
- Screening for HCC is better with US+AFP than US alone
- MRI or alternating US and CT may be cost effective in high risk groups

Conclusions, cont

- Elastography may be useful prior to surgical treatments to predict risk of decompensation or HCC recurrence
- Downstaging to transplant can offer a survival advantage in select patients, but a mandatory waiting time and AFP at time of transplant are important predictors of recurrence
- Care should be taken to stop TACE before liver dysfunction so patients are well enough to receive second line treatments
- Nivolumab had a good safety profile in patients with CTP B, and in the small percentage that responded to treatment there was a good chance of recompensation