



Effectiveness of HCC Surveillance

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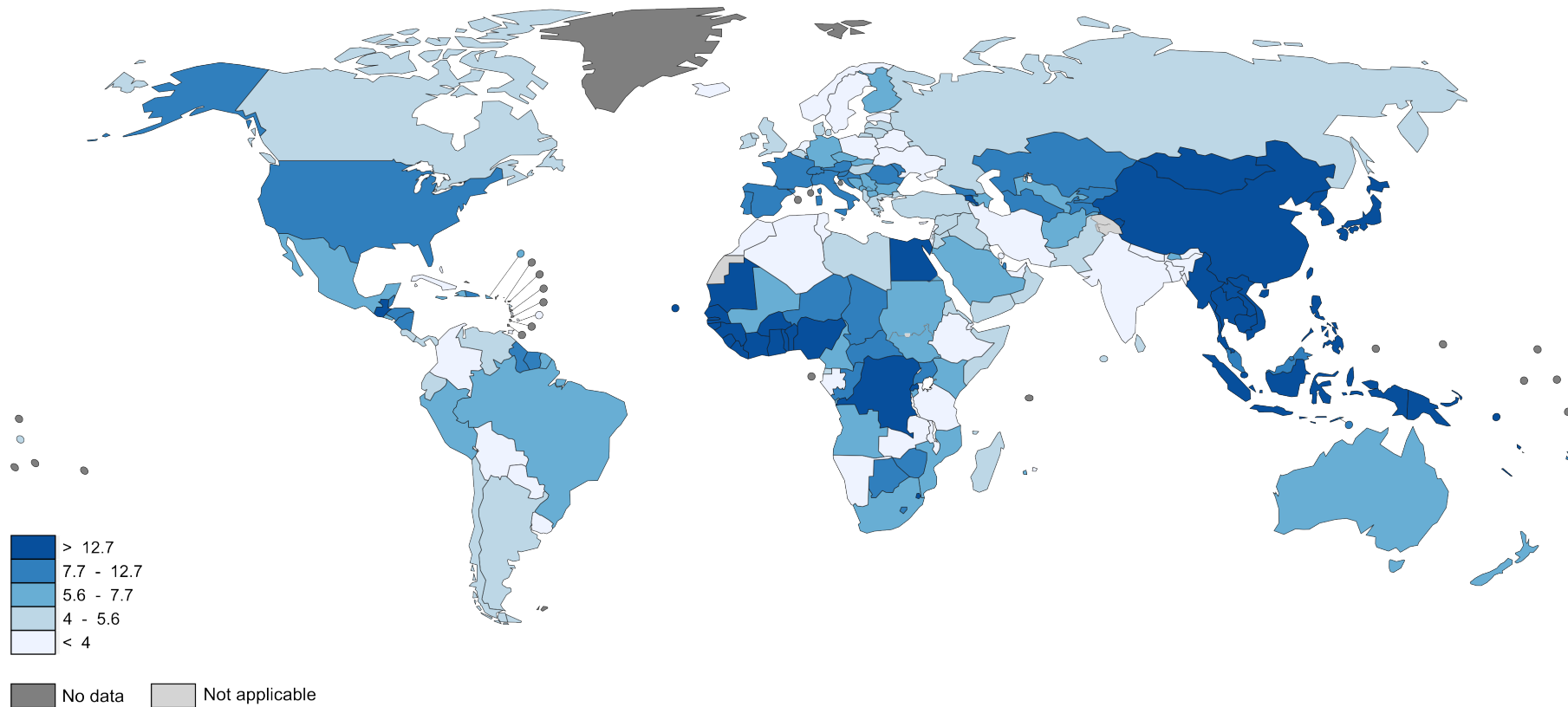
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Disclosures

- I have served on advisory boards or as a consultant for, Bayer, Wako Diagnostics, Exact Sciences, Glycotest, GRAIL, and Roche

Hepatocellular carcinoma is 4th leading cause of cancer-related death worldwide



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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

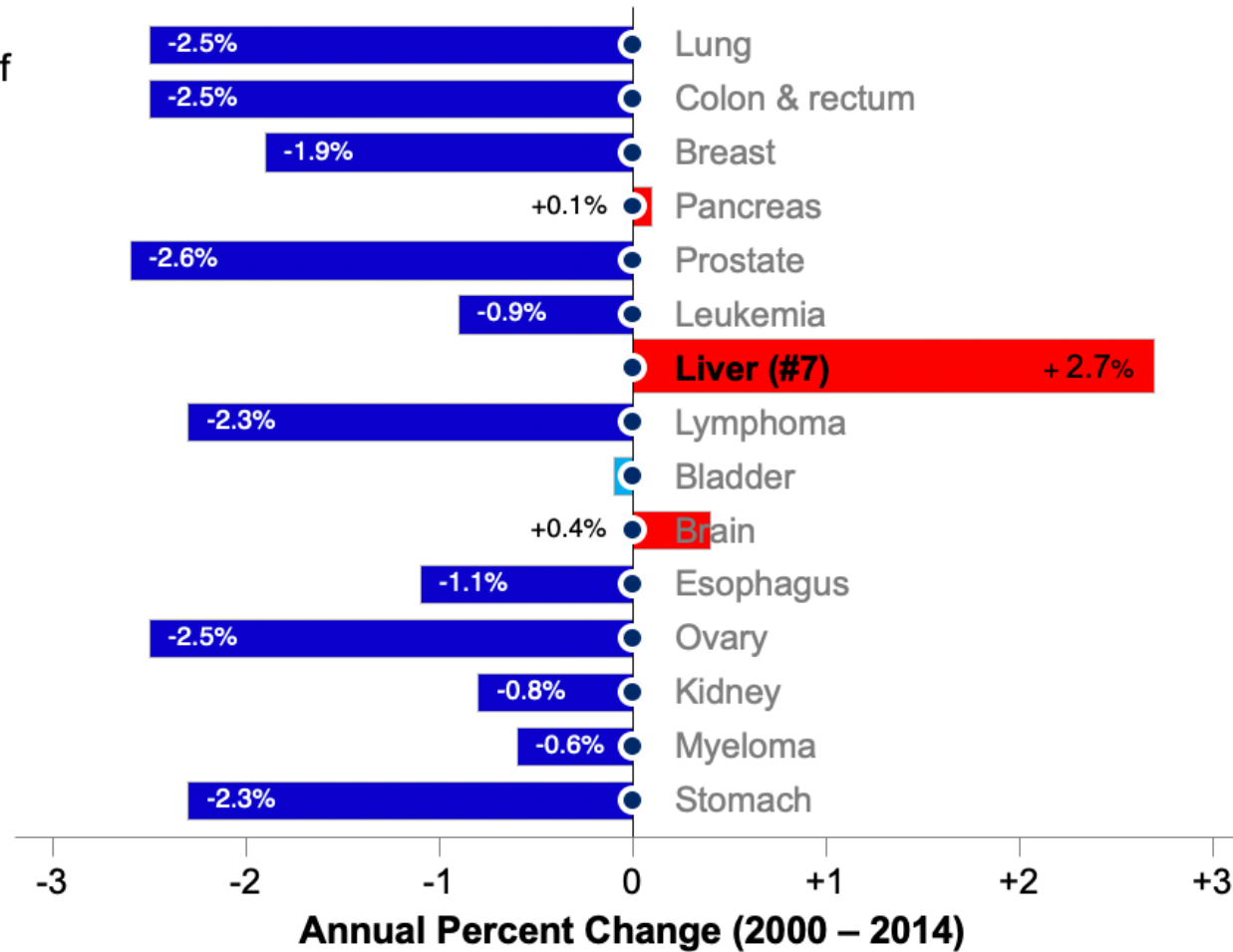


**World Health
Organization**

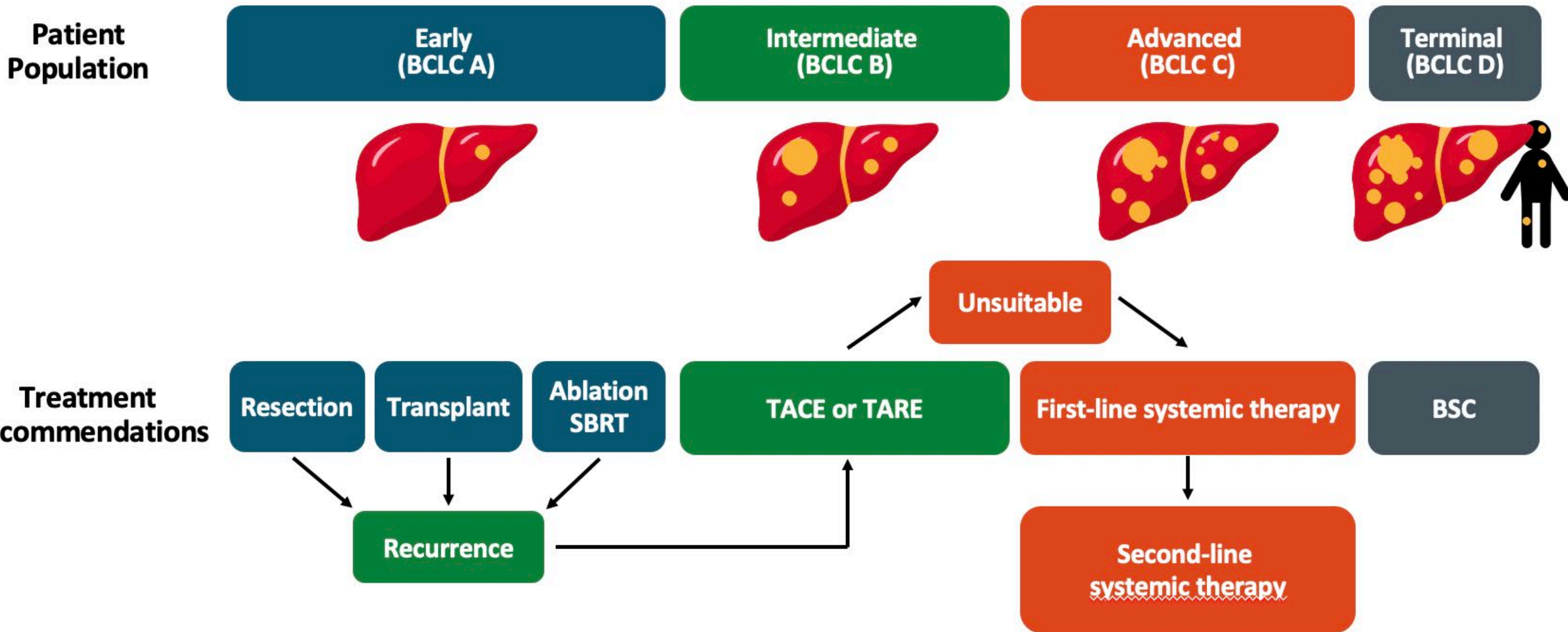
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HCC-related mortality is increasing in the United States

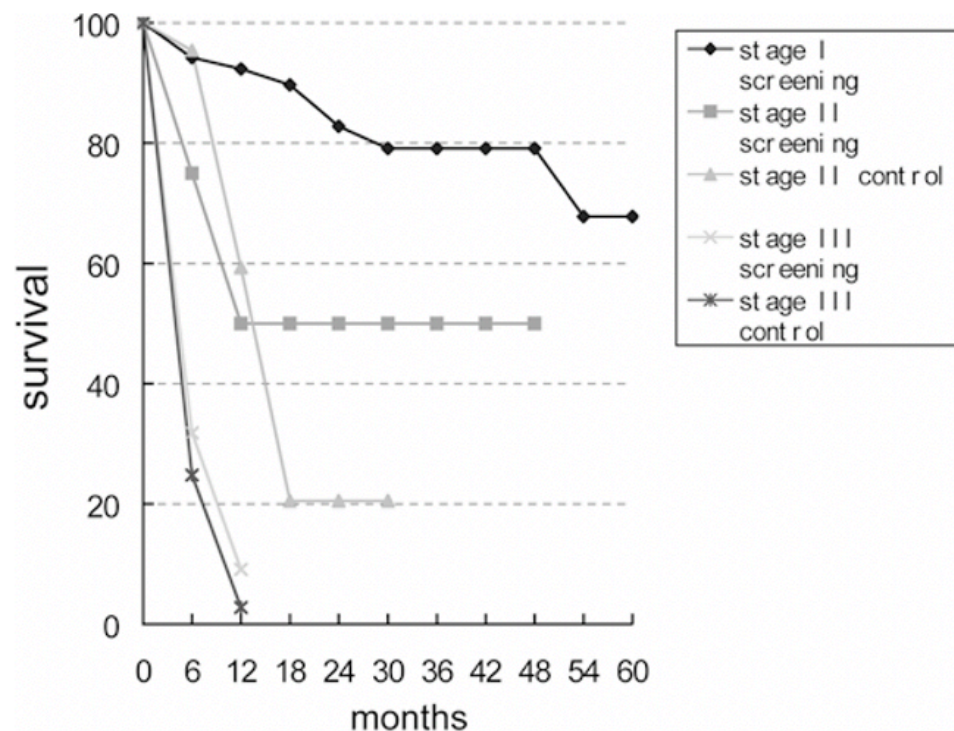
Top 15 causes of cancer death United States 2010-2014



Curative treatment options exist for early stage HCC



HCC surveillance reduces mortality in patients with chronic hepatitis B

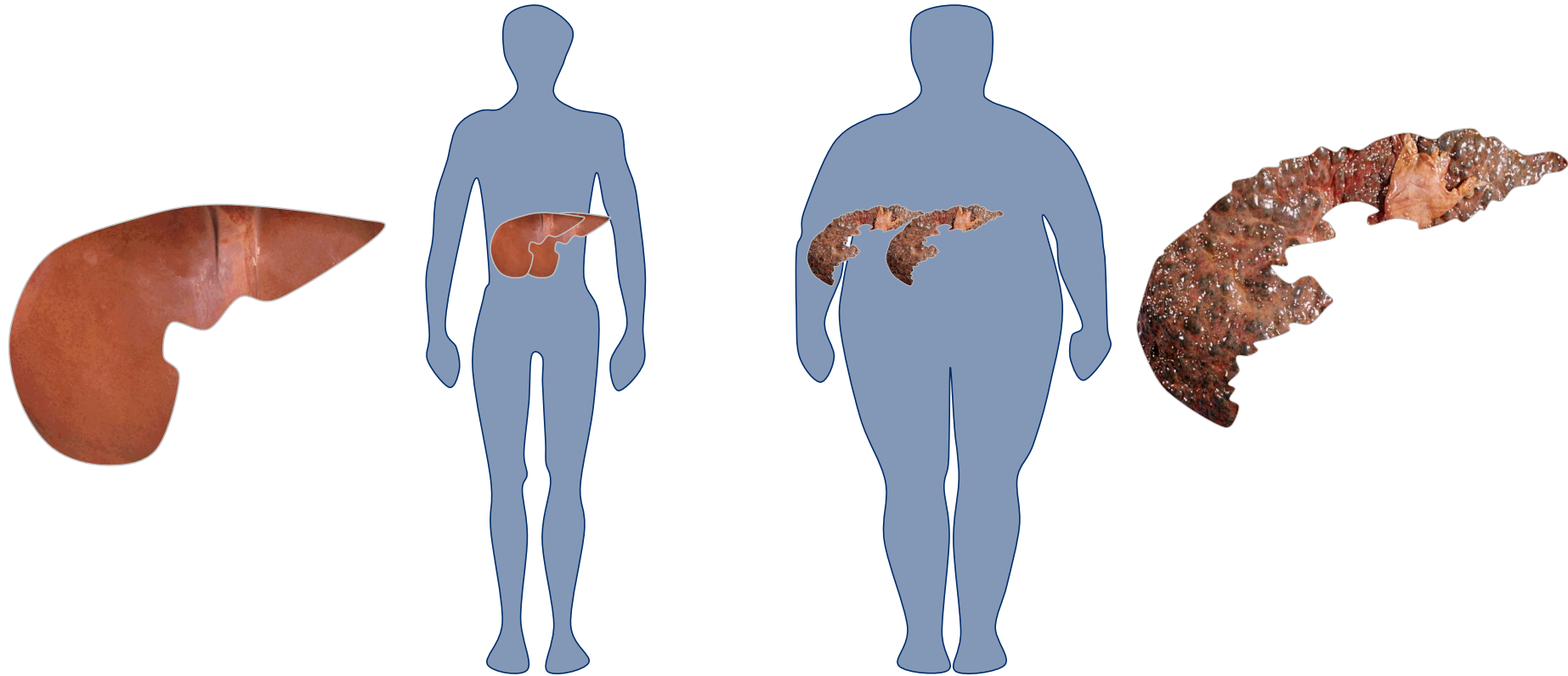


Variable	Screen Group (n=9373)	Control Group (n=9443)
HCC cases	86	67
% Stage I	60.5%	0%
% Curative treatment	46.5%	7.5%
# HCC death	32	54
Mortality (per 100,000)	83.2	131.5
Rate Ratio	0.63 (0.4-0.9)	

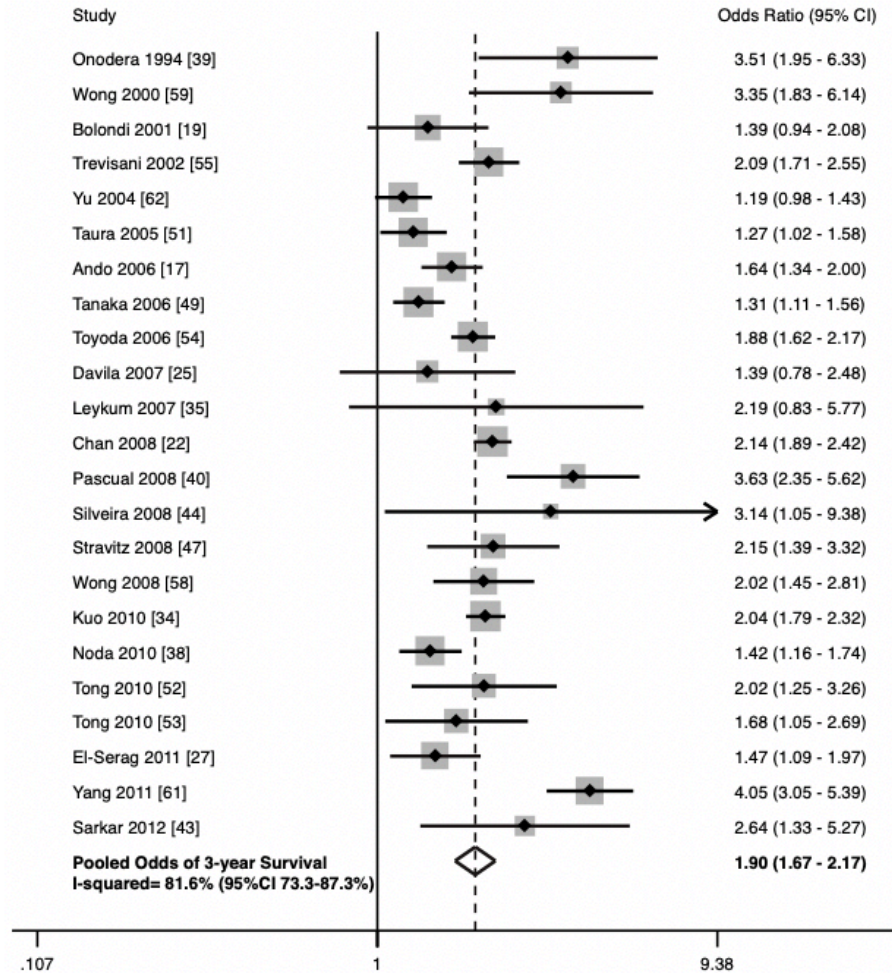
These results may not apply to contemporary U.S. population

Chinese screening population in 1990s

U.S. screening population now



HCC surveillance associated with early detection and improved survival in patients with cirrhosis



Identified 47 studies with 15,158 patients – 6284 (41.4%) detected by surveillance

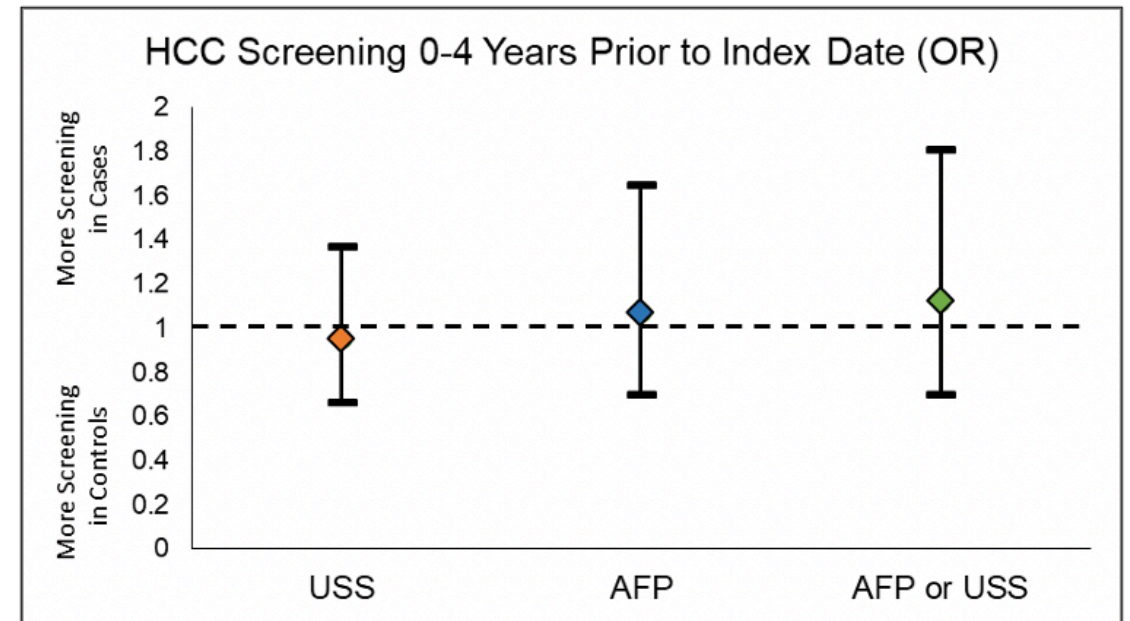
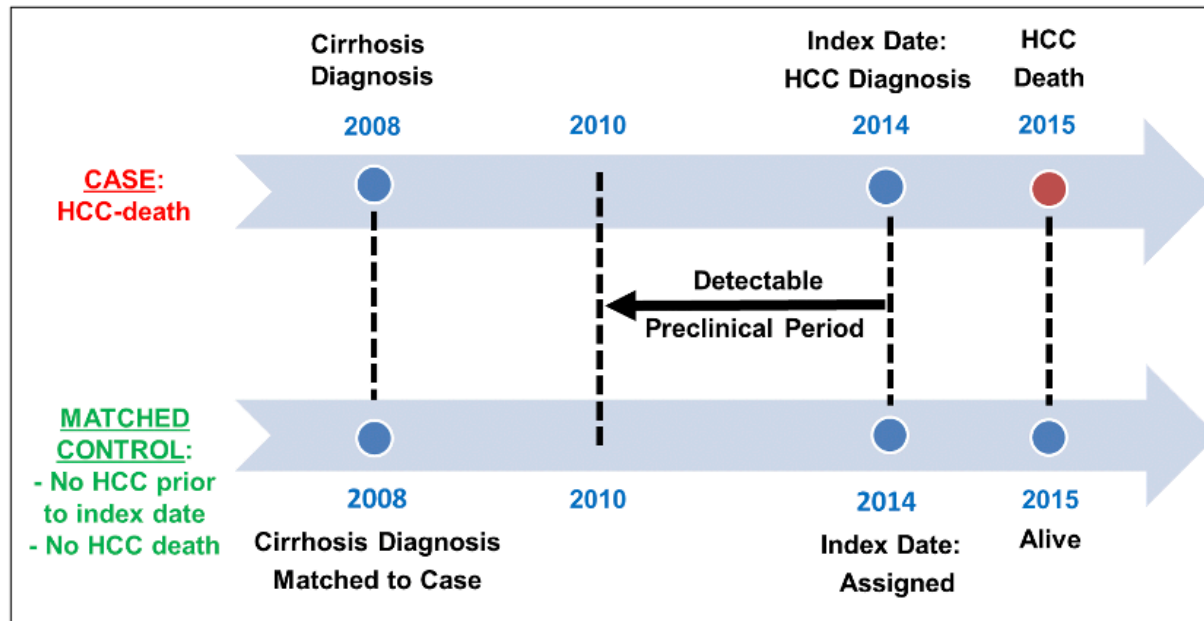
Surveillance associated with:

- Early detection: OR 2.08, 95%CI 1.80 – 2.37
- Curative treatment: OR 2.24, 95%CI 1.99 – 2.52
- Improved survival OR 1.90, 95%CI 1.67 – 2.17

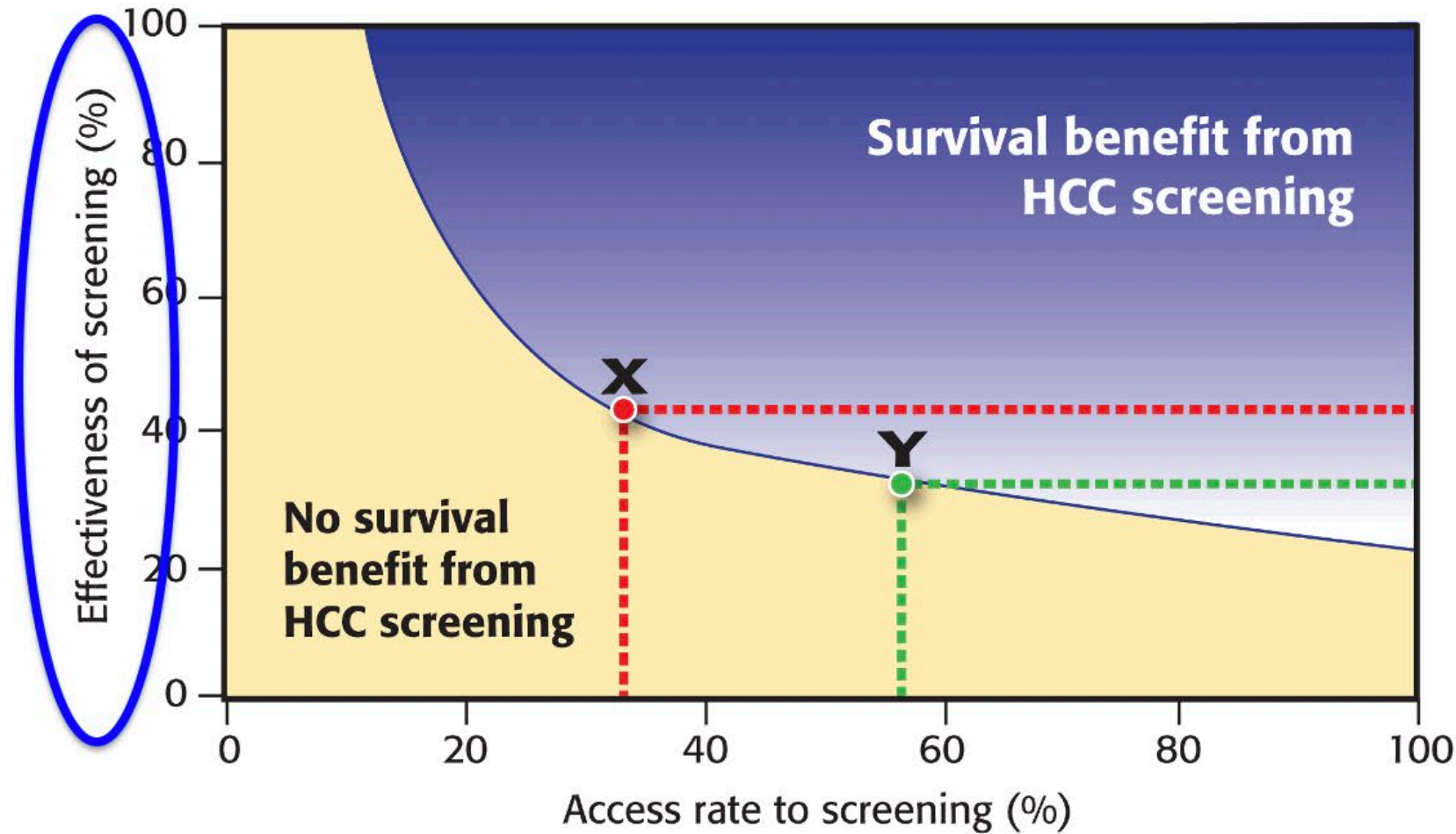
Survival benefit persisted in studies adjusting for lead time bias

Recent data questioning effectiveness of HCC surveillance

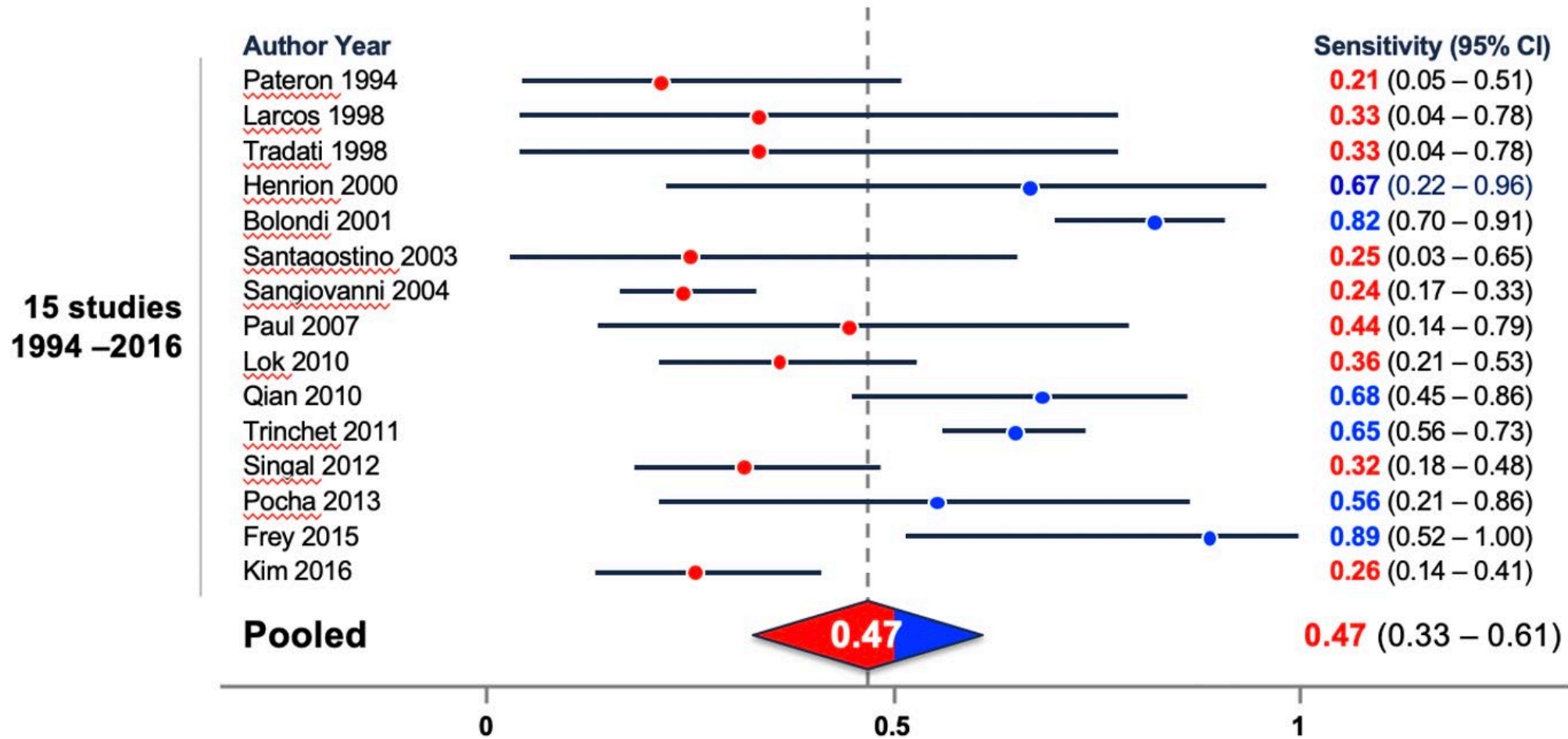
N=238 cases and 238 controls



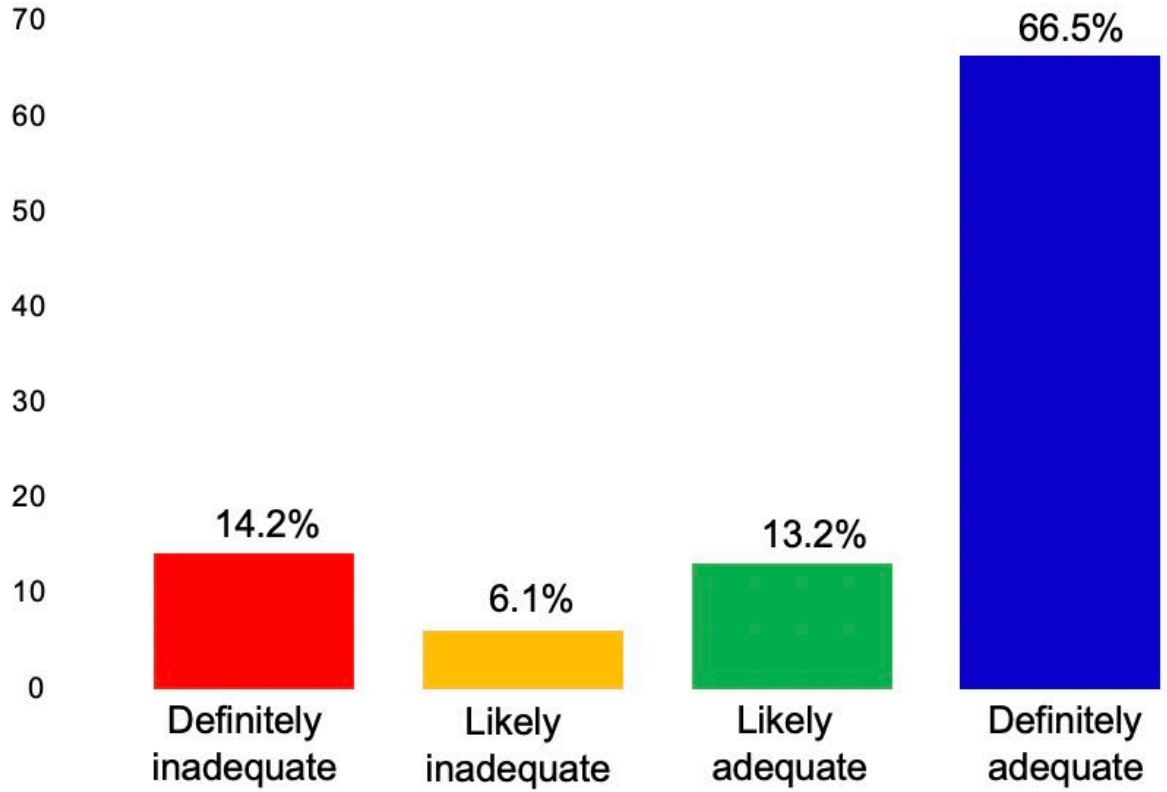
Test effectiveness and screening access are critical to HCC surveillance reducing mortality




Ultrasound alone has poor sensitivity for early HCC detection



Nearly 1 in 5 ultrasounds suboptimal visualization for HCC surveillance



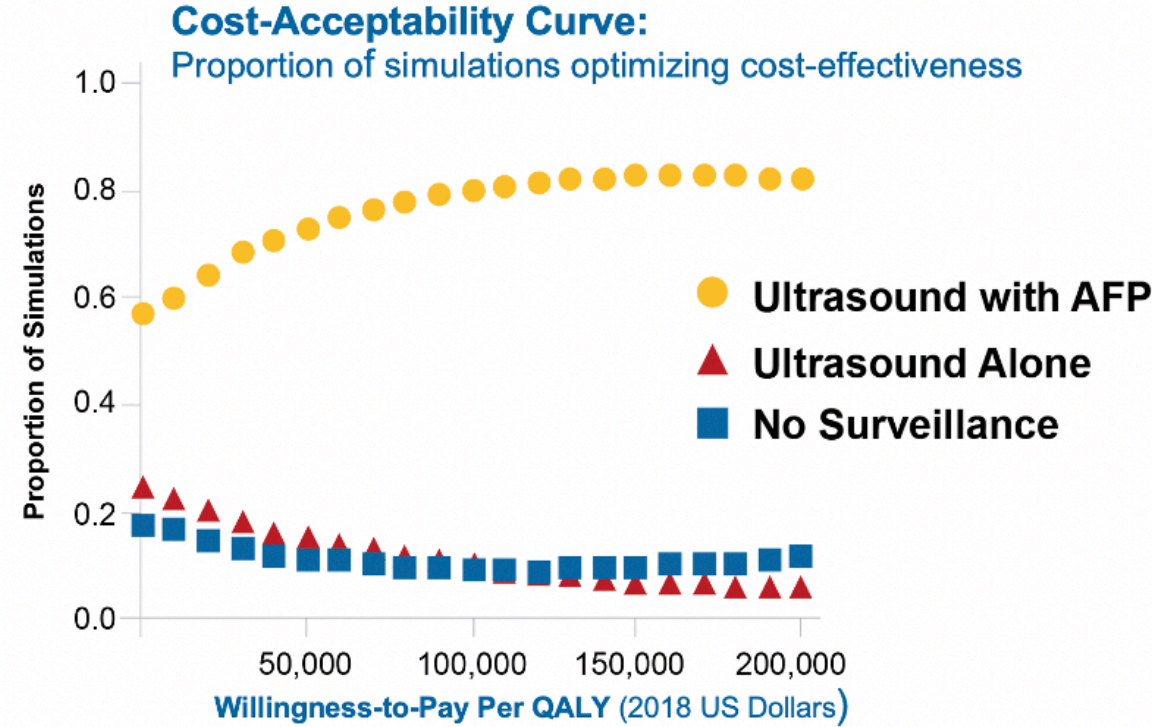
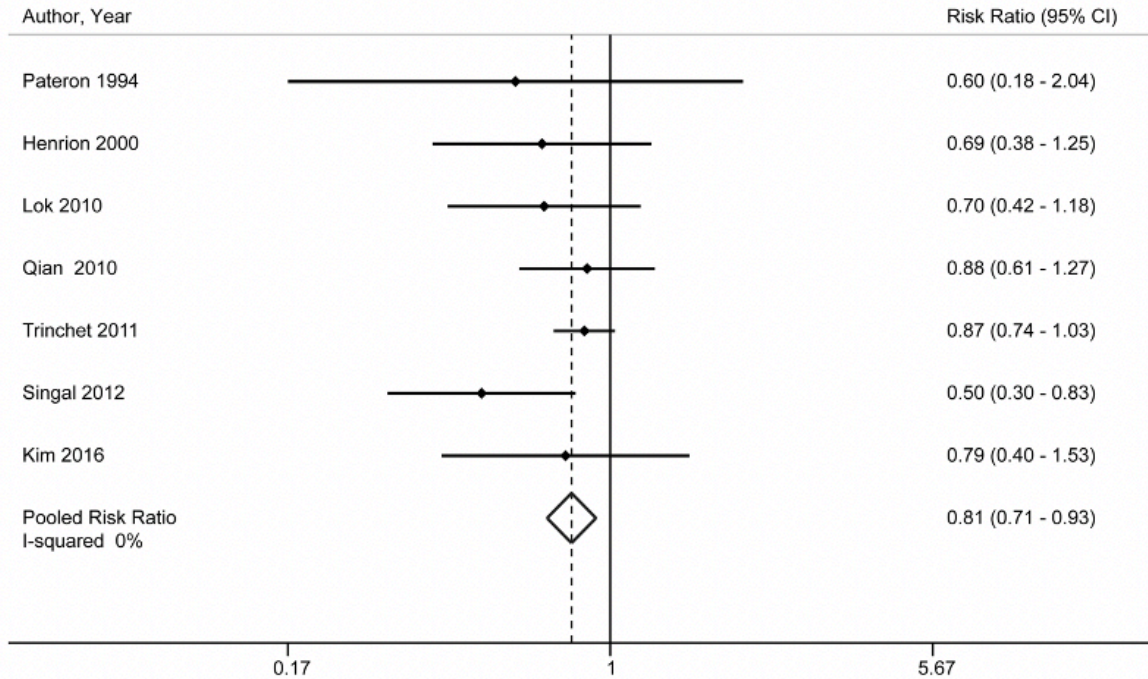

Child Pugh B/C
 OR 1.65 (1.06 – 2.57)


Obesity
 OR 2.60 (1.36 – 4.97)
Morbid Obesity
 OR 8.86 (4.02 – 19.5)


Alcohol-related cirrhosis
 OR 1.84 (1.09 – 3.09)


NASH cirrhosis
 OR 2.48 (1.30 – 4.75)

AFP appears to be of benefit for early HCC detection



Sensitivity of US with vs without AFP for early-stage HCC:
63% vs. 45% ($p=.002$)

GALAD is a promising novel biomarker panel for early detection

- GALAD: **G**ender, **A**ge, **A**FP-L3, **A**FP, and **D**CP
- Multi-national nested case control with 6834 patients (2430 HCC, 4404 CLD)

Variable	Sensitivity	Specificity	Correctly classified
UK cohort (all)	91.6%	89.7%	90.6%
UK cohort (Milan)	80.2%	89.7%	87.9%
Japan cohort (all)	70.5%	95.8%	87.2%
Japan cohort (Milan)	60.6%	95.8%	87.7%
Germany cohort (all)	87.6%	88.6%	88.3%
Germany cohort (<u>unifocal</u> < 5cm)	67.4%	88.6%	87.5%

No difference in GALAD performance by cirrhosis etiology, SVR, or HBV treatment

Methylated DNA marker panels also show promise for early HCC detection

Biomarker Test	Sensitivity, % (95% CI)			Specificity % (95% CI)
	Any Stage [n = 136]	BCLC 0 + A [n = 81]	Milan Criteria [n = 71]	
Exact Sciences	81 (74 – 87)	70 (60 – 80)	68 (56 – 78)	89 (86 – 92)
AFP (≥7.7 ng/mL)	64 (56 – 72)	52 (41 – 63)	46 (35 – 59)	89 (86 – 92)
AFP (20 ng/mL)	46 (38 – 55)	31 (21 – 42)	27 (17 – 39)	98 (96 – 99)

MRI is more sensitive for early tumor detection but may be limited by cost effectiveness

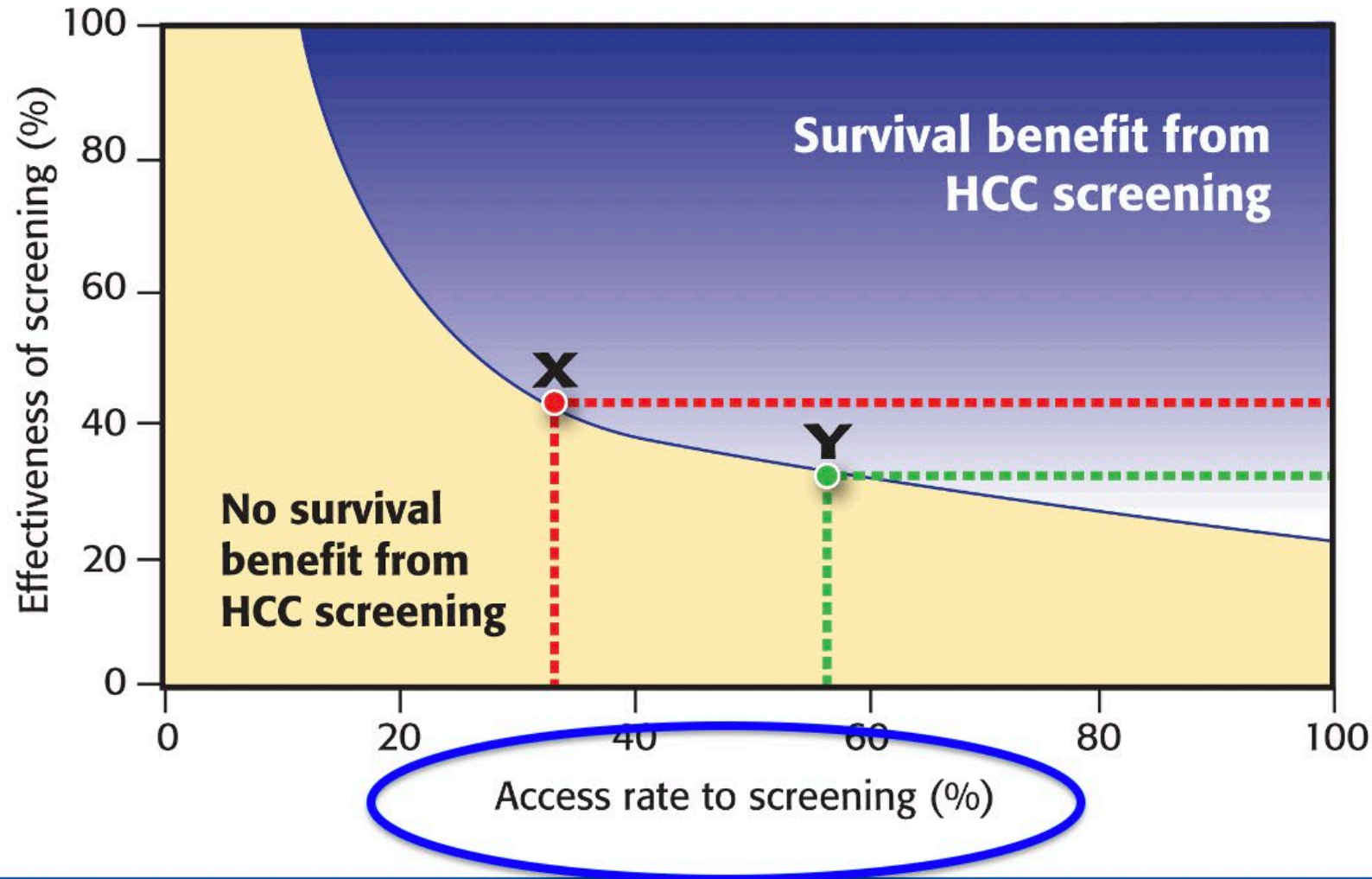
- Prospective study with 407 Child A-B patients (majority HBV-infected)
 - 1112 surveillance rounds over 1.5 years
 - Semi-annual ultrasound and MRI done in all patients
- 43 patients diagnosed with HCC
 - 32 very early stage and 10 early stage HCC

Cohort	MRI	US	P-value
Sensitivity	86%	28%	P<0.001
Sensitivity for BCLC 0	86%	26%	P<0.001
Specificity	97%	94%	P=0.004

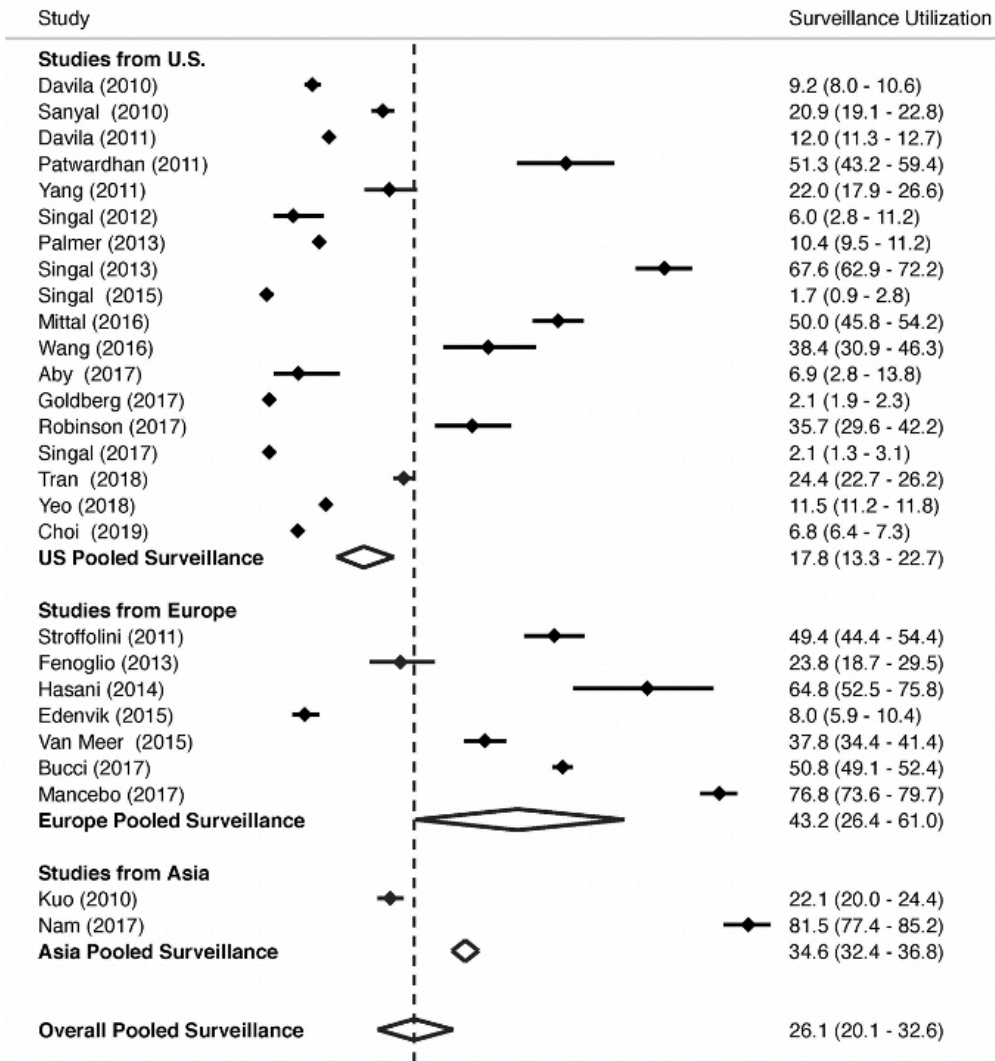
Early data suggest abbreviated MRI can achieve high accuracy

Study	UCSD-Duke ¹	Mount Sinai ²	UCSD ³	UTSW ⁴
N	298	174	79	86
Design	Hepatobiliary AMRI	Hepatobiliary AMRI	Hepatobiliary AMRI	Dynamic AMRI
Population	cirrhosis, screening	mixed, screening / diagnostic	cirrhosis, screening	cirrhosis, diagnostic
Reference Std.	composite	histopathology	composite	composite
# Readers	2	2	2	5
Sensitivity	83.7 [71.7-90.9]	80.6 [70.7-87.8]	85.2 [72.8-93.3]	92.1 [86.4-95.6]
Specificity	93.2 [90.0-95.6]	96.1 [92.3-98.1]	92.2 [87.0-95.8]	88.6 [84.4-91.8]

Test effectiveness and screening access are critical to HCC surveillance reducing mortality



HCC surveillance is underused in clinical practice



Identified 29 studies between Jan 2010 – Aug 2018

Pooled surveillance estimate was only 26.1%

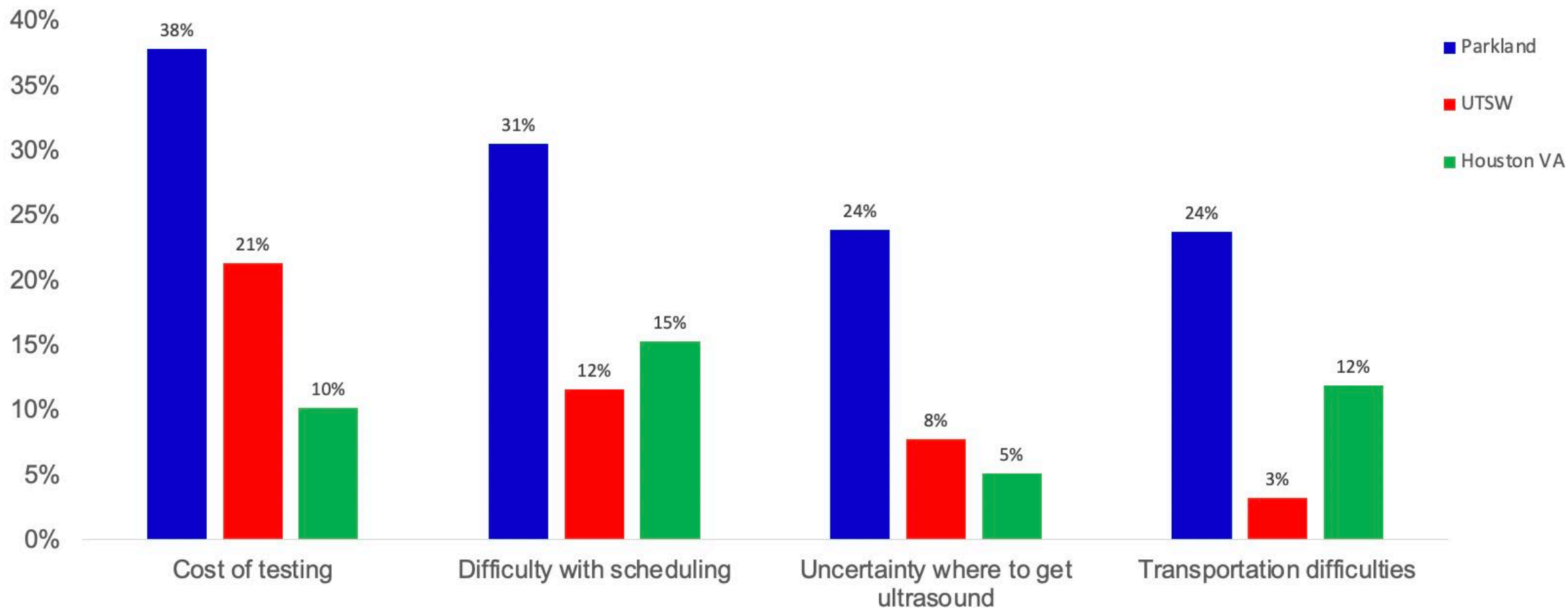
- Lower surveillance in US studies vs. Europe and Asia (17.8% vs. 43.2% and 34.6%)
- Higher surveillance in GI/Hepatology clinics vs. academic primary care clinics and population-based cohorts (73.7% vs. 29.5% and 8.8%)

Consistent correlates included higher surveillance with GI/Hepatology subspecialty care and increased number of clinic visits and lower surveillance in patients with NASH or alcohol-related cirrhosis.

Providers report potential barriers to HCC surveillance

Provider-reported barriers	Safety-net health system (n=77)	Tertiary care system (n=100)
Lack of knowledge about guidelines	68.2%	79.1%
Competing interests in clinic	51.6%	37.4%
Lack of time in clinic	40.5%	52.8%
Difficulty recognizing at-risk patients	35.4%	30.0%
Ultrasound capacity	23.0%	10.1%
Responsibility of subspecialists > PCP	5.3%	29.4%

Patients report barriers to HCC surveillance



Presence of barriers independently associated with reduced HCC surveillance (aOR 0.62, 95%CI 0.41 – 0.94)

In-reach and outreach interventions can significantly increase HCC surveillance

Author, year	Study Setting	Study Period	Intervention	Outcome	Pre-Intervention [n (%)]	Post-Intervention [n (%)]	Absolute Difference	Relative Difference
Aberra 2013	U. Michigan, USA	2008-2011	Nurse base protocol	One-time abdominal imaging	119/160 ^b (74.4)	331/355 (93.2)	18.8%	25.3%
Kennedy, 2013	Flinders Medical Center, Australia	2007-2009	PCP and patient education, system redesign	Semi-annual US and AFP for two years	0/22 (0)	14/22 (63.6)	63.6%	-
Beste, 2015	Northwest Veterans Affairs, USA	2011-2012	EMR Reminder	≥2 abdominal imaging within 18 months	103/564 (18.2)	218/790 (27.6)	9.4%	51.6%
Del Poggio, 2015	120 PCPs, Italy	1994-2013	PCP Education	HCC diagnosed by surveillance	85/244 (34.8)	105/190 (55.3)	20.5%	58.9%
Nazareth 2016	Royal Perth Hospital, Australia	2010-2015	Nurse-led clinic	Semi-annual ultrasound	-	40/76 (52.6)	-	-
Farrell 2017	Royal Liverpool Hospital, UK	2009-2013	Radiology led recall	Semi-annual US	-	368/804 (45.8)	-	-
Bui 2017	KP Northern California, USA	Not reported	EMR identification and physician extender	3 abdominal imaging in 2 years	51/224 (22.8)	183/224 (81.7)	58.9%	258.3%
Singal, 2019	Parkland, Dallas, TX	2014-2016	Mailed outreach	Semi-annual US over 18 months	44/600 (7.3)	247/1200 (20.6)	13.3%	182.2%

Summary

- HCC surveillance supported by RCT in patients with chronic HBV and several cohort studies in those with cirrhosis
- Test accuracy and surveillance utilization are key factors for effectiveness
- Ultrasound has suboptimal sensitivity, particularly in contemporary cohorts
 - Novel blood- and imaging-based modalities are being evaluated
- Surveillance is underused in clinical practice due to patient- and provider-barriers
 - Intervention strategies show promise to increase utilization

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