BMUS

Chronic liver disease and HCC

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BMUS

Aims

- Background on HCC in chronic liver disease
- Role of surveillance
  - Who, how and why
- Challenges and limitations of surveillance
- HCC treatment paradigm

Mortality from liver disease is rising

Mortality from Major Disease

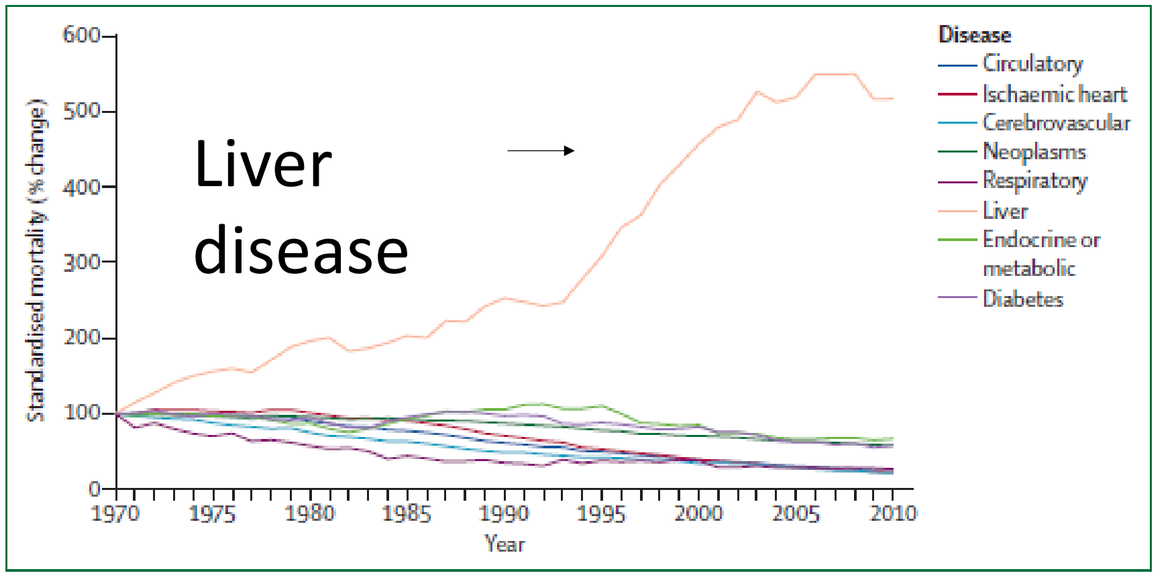
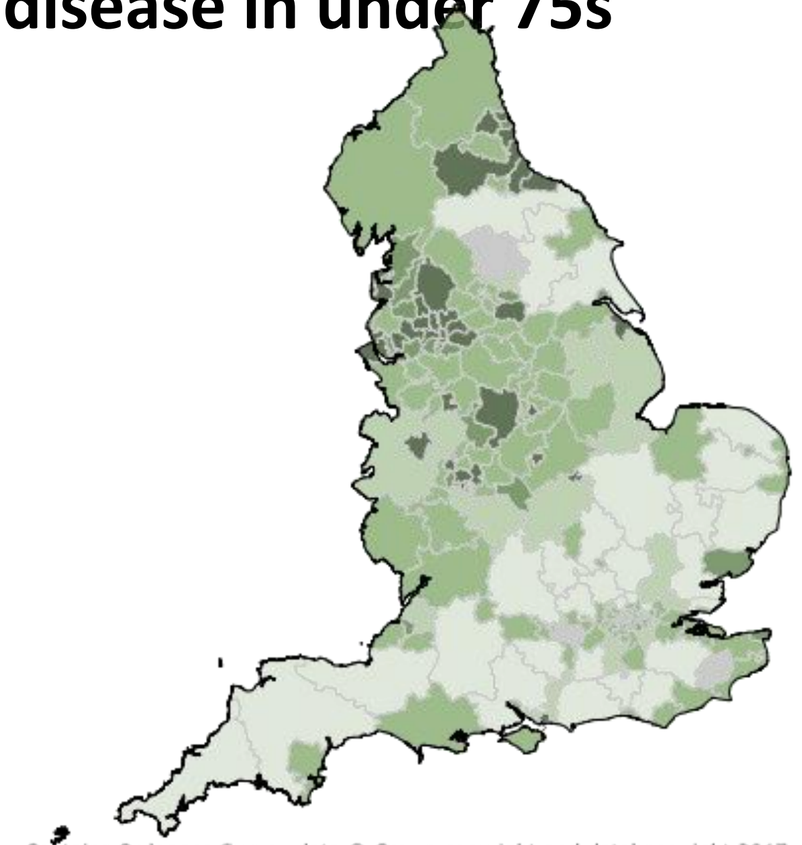


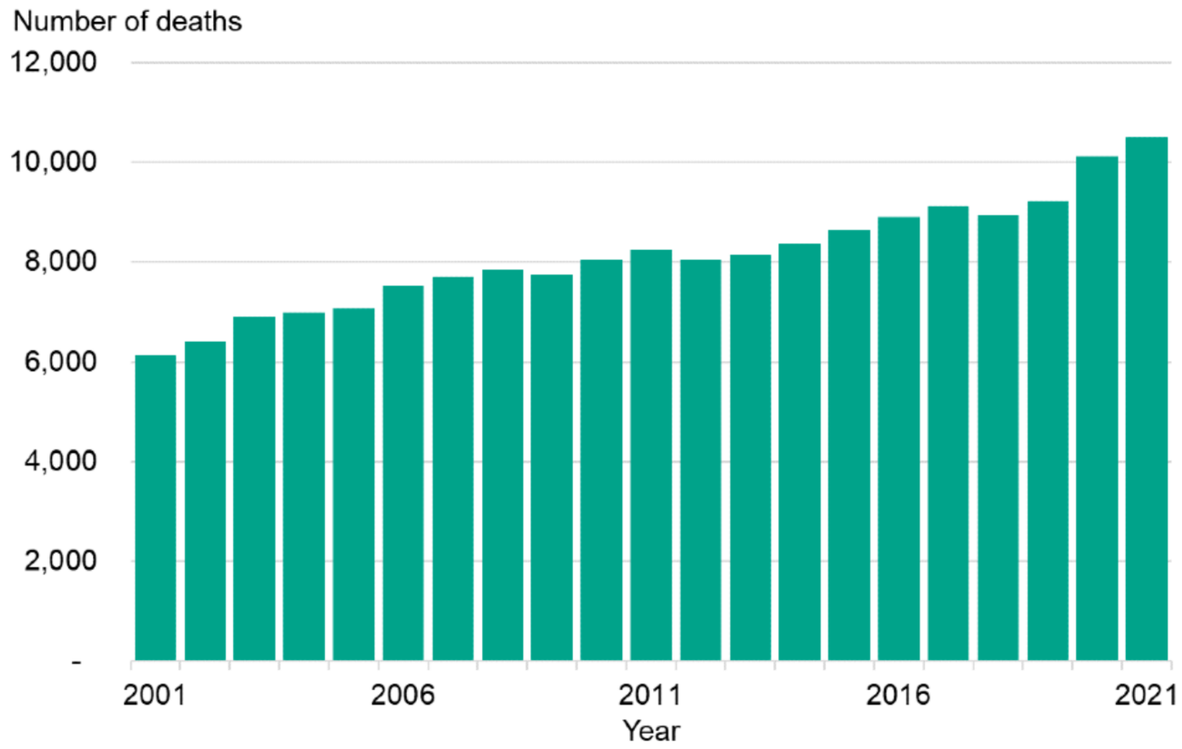
Figure 1: Standardised UK mortality rate data
Data were normalised to 100% in 1970, and subsequent trends plotted using the software Statistical Package for the Social Sciences. Data are from the WHO-HFA database.[4] Analysed by Nick Sheron (September, 2013).

Mortality from liver disease in under 75s

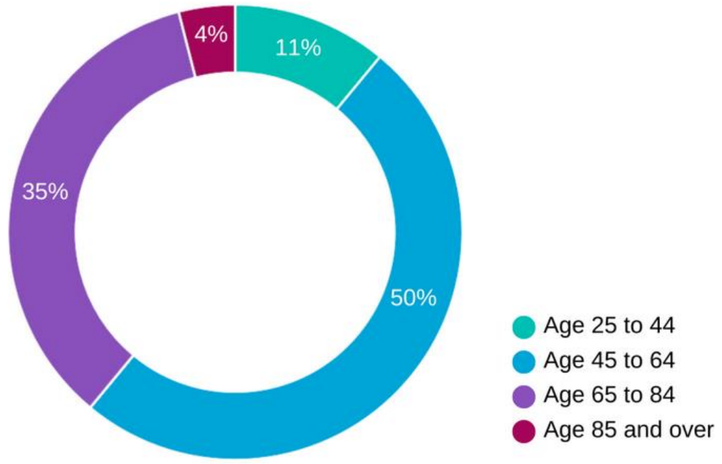


Williams et al

Figure 1: number of deaths from liver disease in persons aged under 75, England, 2001 to 2021



- 64% increase from liver disease over last 20 years.
- NW highest number (1932) of deaths from premature liver disease
- Alcohol > MASLD



Liver disease deaths by age group

UK.Gov. https://www.gov.uk/government/statistics/liver-disease-profiles-march-2023-update/liver-disease-profiles-march-2023-update Accessed June 2024

Reasons for rising rates of liver deaths

Cirrhosis is frequently diagnosed late

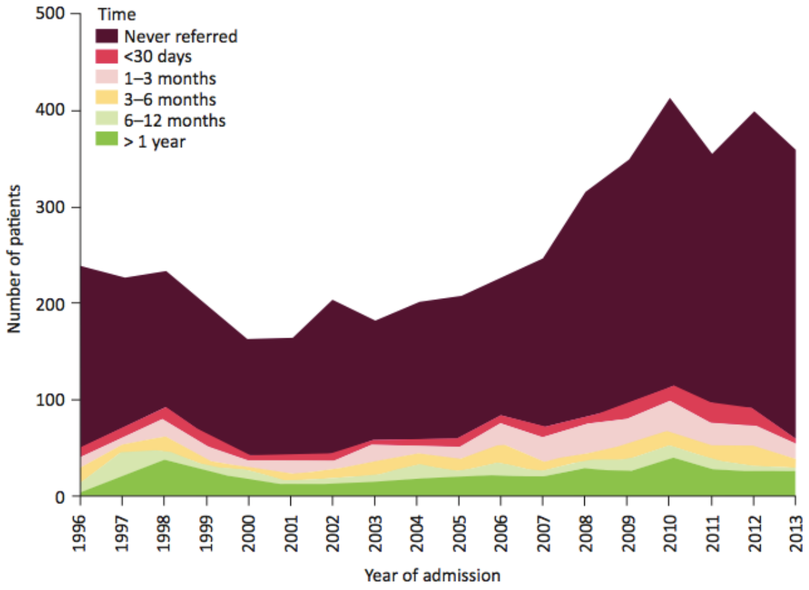


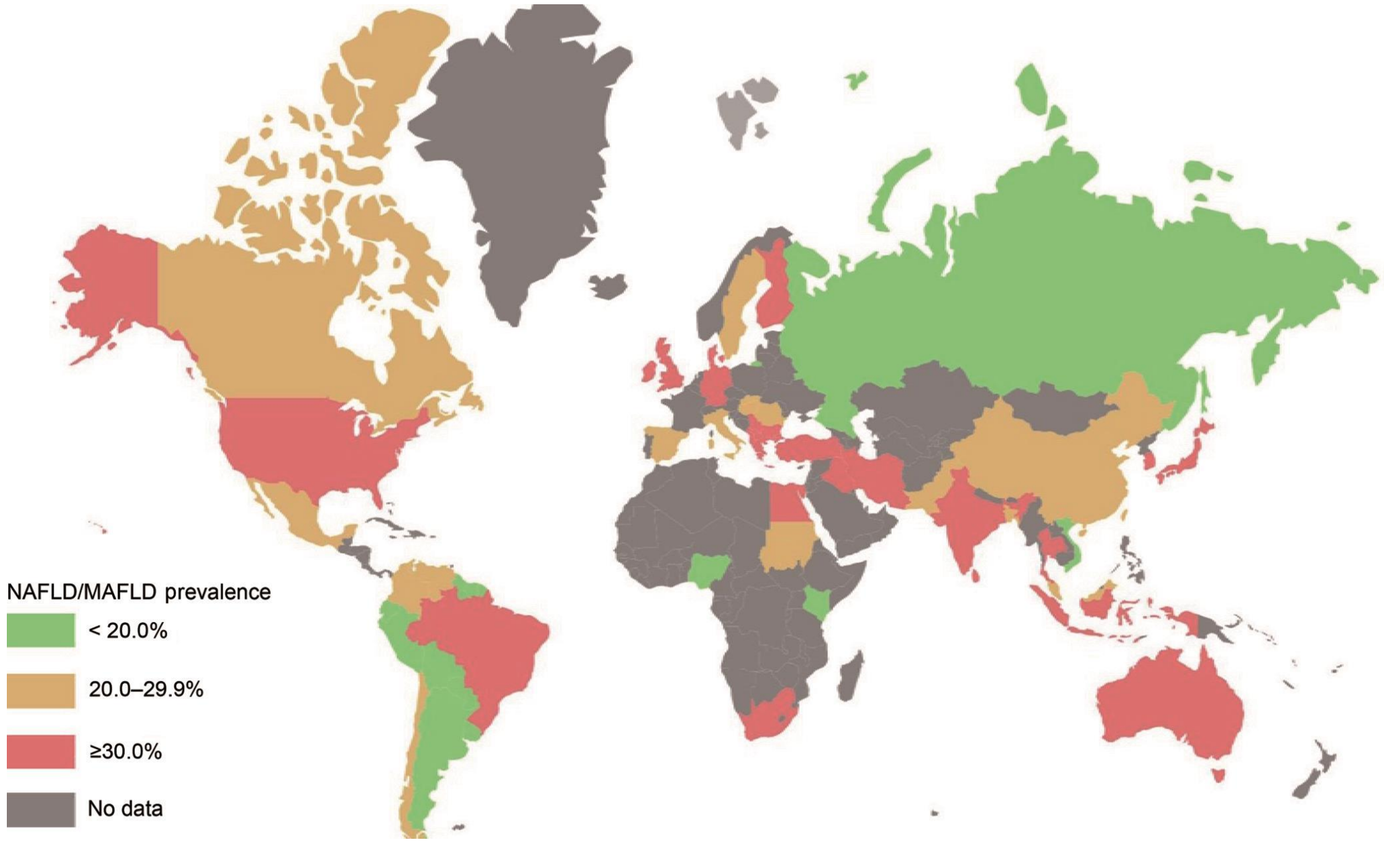
Fig 2. Time period between referral to a liver clinic and the first admission with cirrhosis or liver failure.
Adapted with permission.[1]

- High levels of harmful drinking
- Rising obesity rates
- Strong association between liver disease and deprivation

Williams et al
Lancet 2015

WHO Fact Sheet 2022

- 2.5 billion adults >18 years were overweight. 43% of adult global population
- Of these, 890 million were living with obesity. 16% were living with obesity.

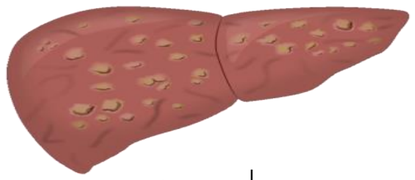


MAFLD Prevalence 2021

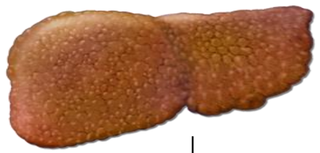
doi: 10.14218/JCTH.2021.00201

https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Natural history for fatty liver disease



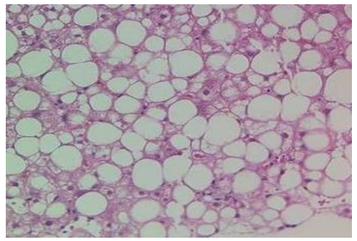
20%



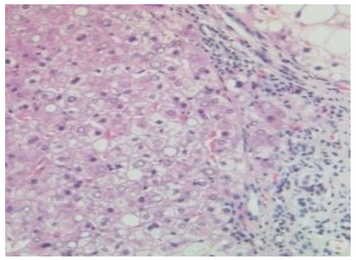
45% risk of **Decompensation** at 10 years

2% risk of **HCC** per year

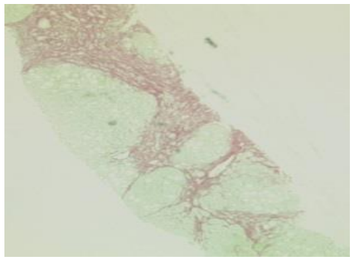
20% mortality At 10 years



Hepatic steatosis
(fatty infiltration of liver)



Steatohepatitis +/- fibrosis
(fat + hepatocellular injury and inflammation)

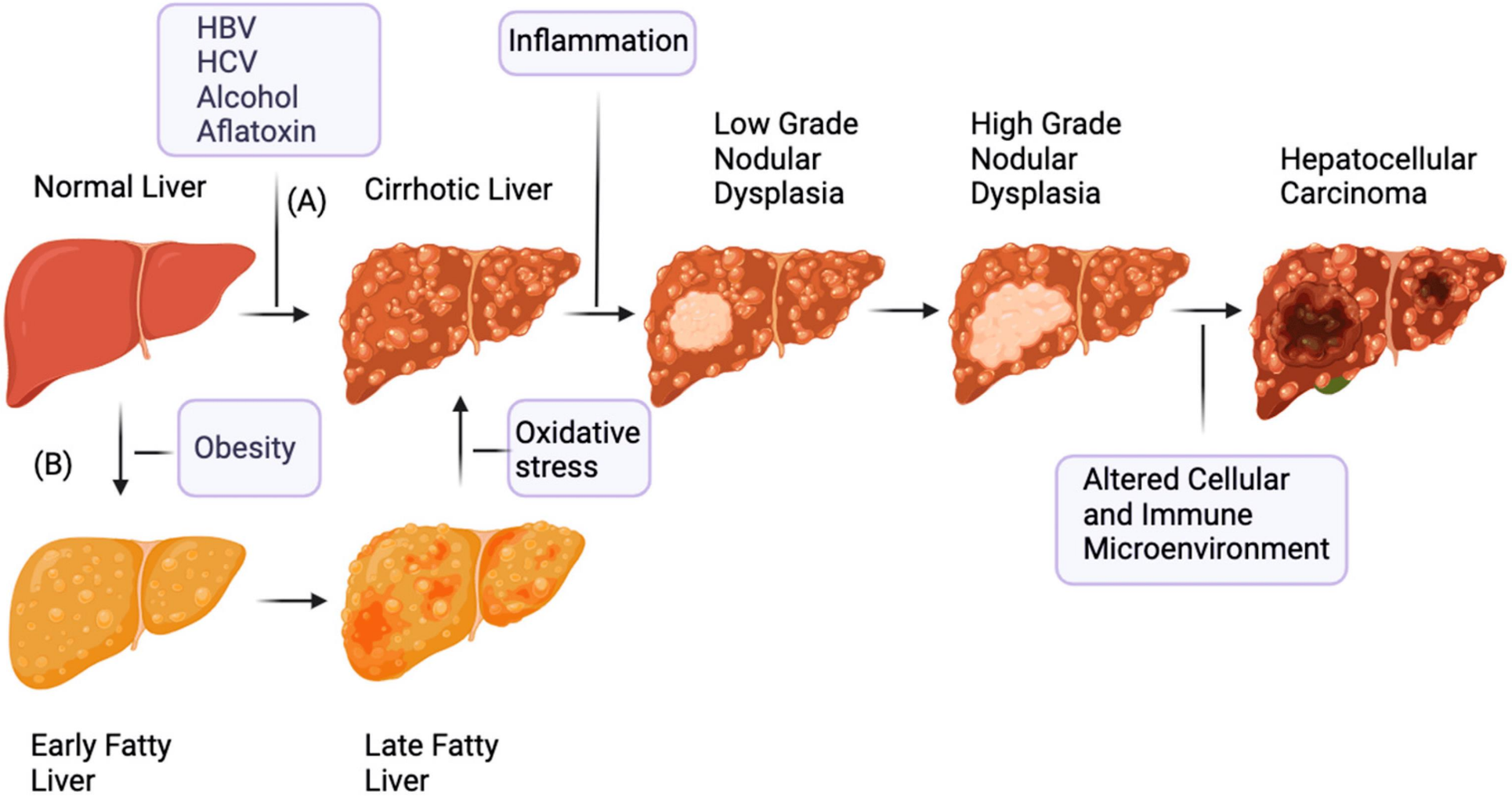


Cirrhosis

Major risk factors for progression

- Obesity
- Type 2 diabetes
- Metabolic syndrome
- Alcohol consumption

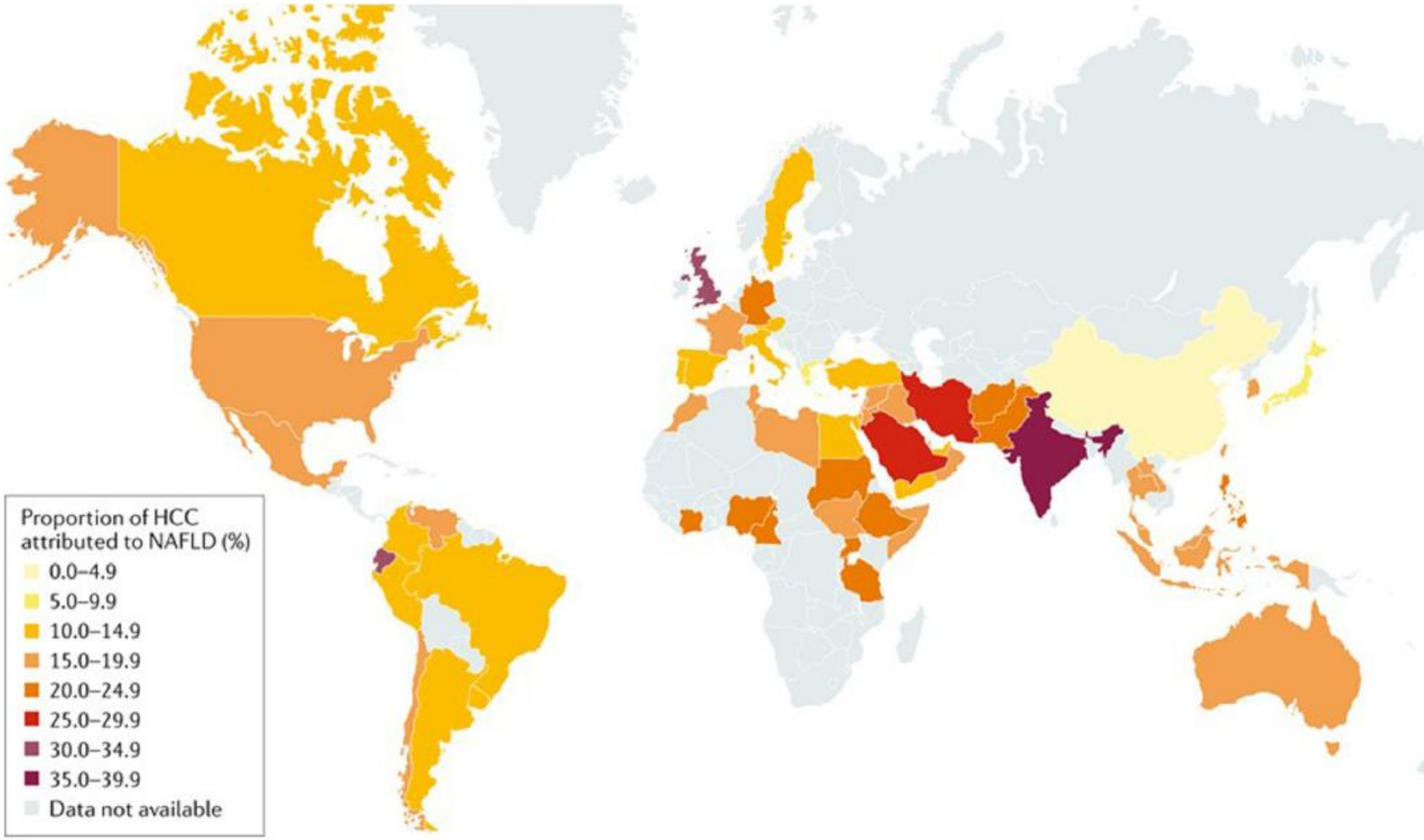
BACKGROUND



Cancer Stage:
Number
Size
Invasion
Metasasis/EHD

Liver function

Proportion HCC attributed MASLD



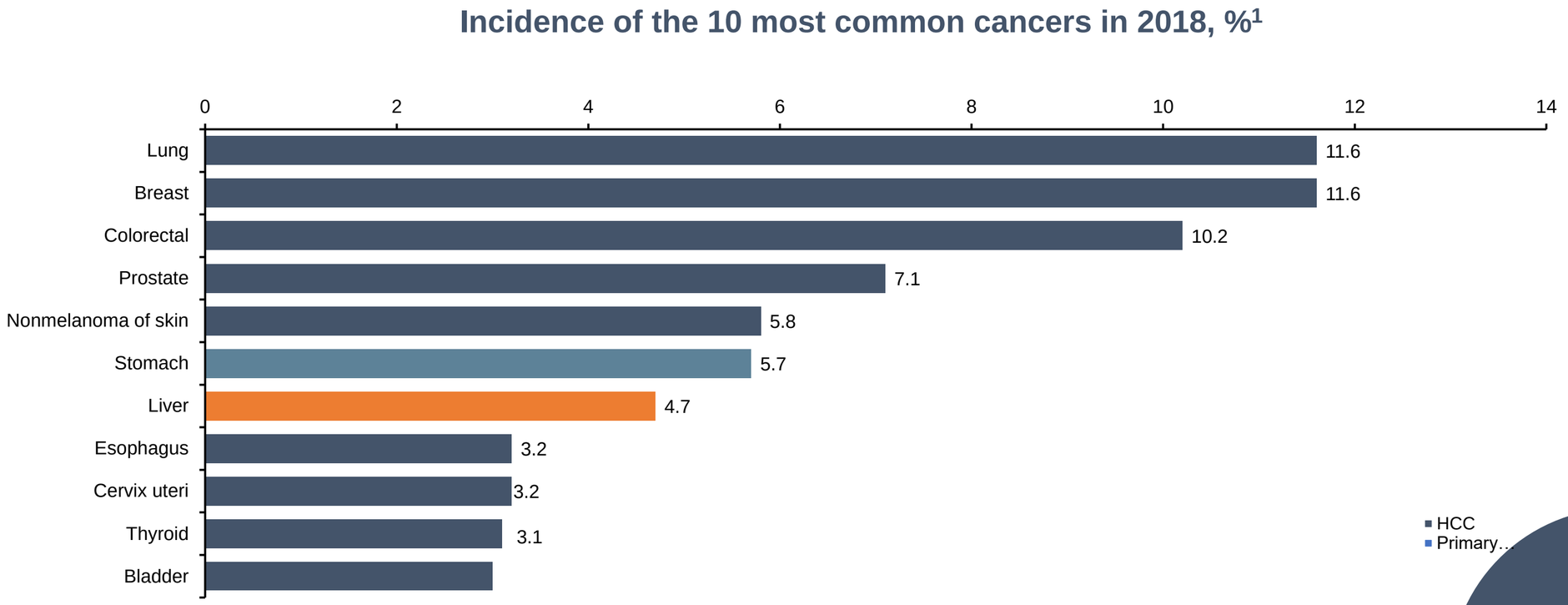
Highest in:

India	35-40%
UK	30-35%
Middle East	20-30%
Australia	15-20%

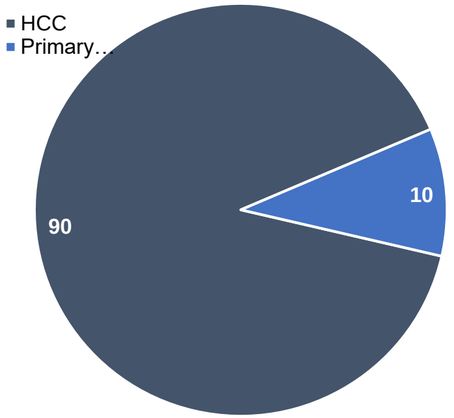
Nat Rev Gastroenterol Hepatol. 2021 April ; 18(4): 223–238. doi:10.1038/s41575-020-00381-6.

Liver cancer is the sixth most common cancer worldwide

It represented 4.7% of all 18.1 million new cancer cases in 2018[1]



HCC is responsible for 90% of all liver cancers[2]



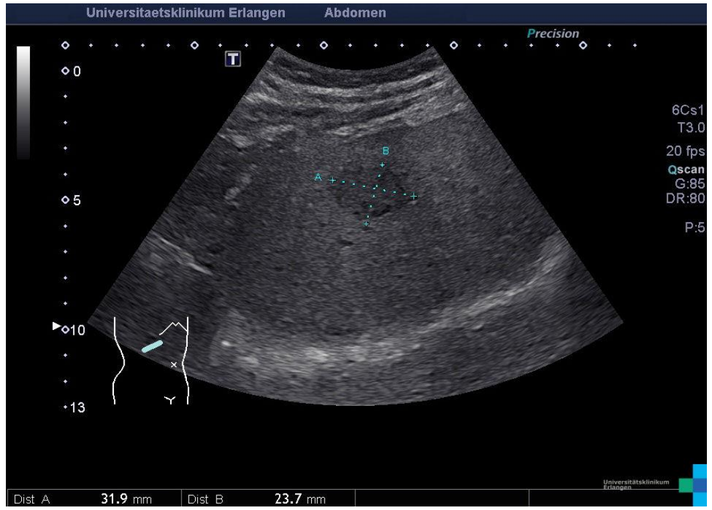
HCC, hepatocellular carcinoma

1. Bray F, et al. CA Cancer J Clin. 2018;68:394-424; 2. Llovet JM, et al. Nat Rev Dis Primers. 2016;2:16018

How do we reduce liver mortality?

- Identifying patients with Liver disease before they develop cirrhosis and intervening with lifestyle modifications/treatments

- Surveillance/monitor for complications of liver disease in those with cirrhosis
  - Decompensation and management
  - HCC
  - Varices
  - Transplantation
  - Palliation



Newcastle University | Centre for Cancer

HCC Milestones

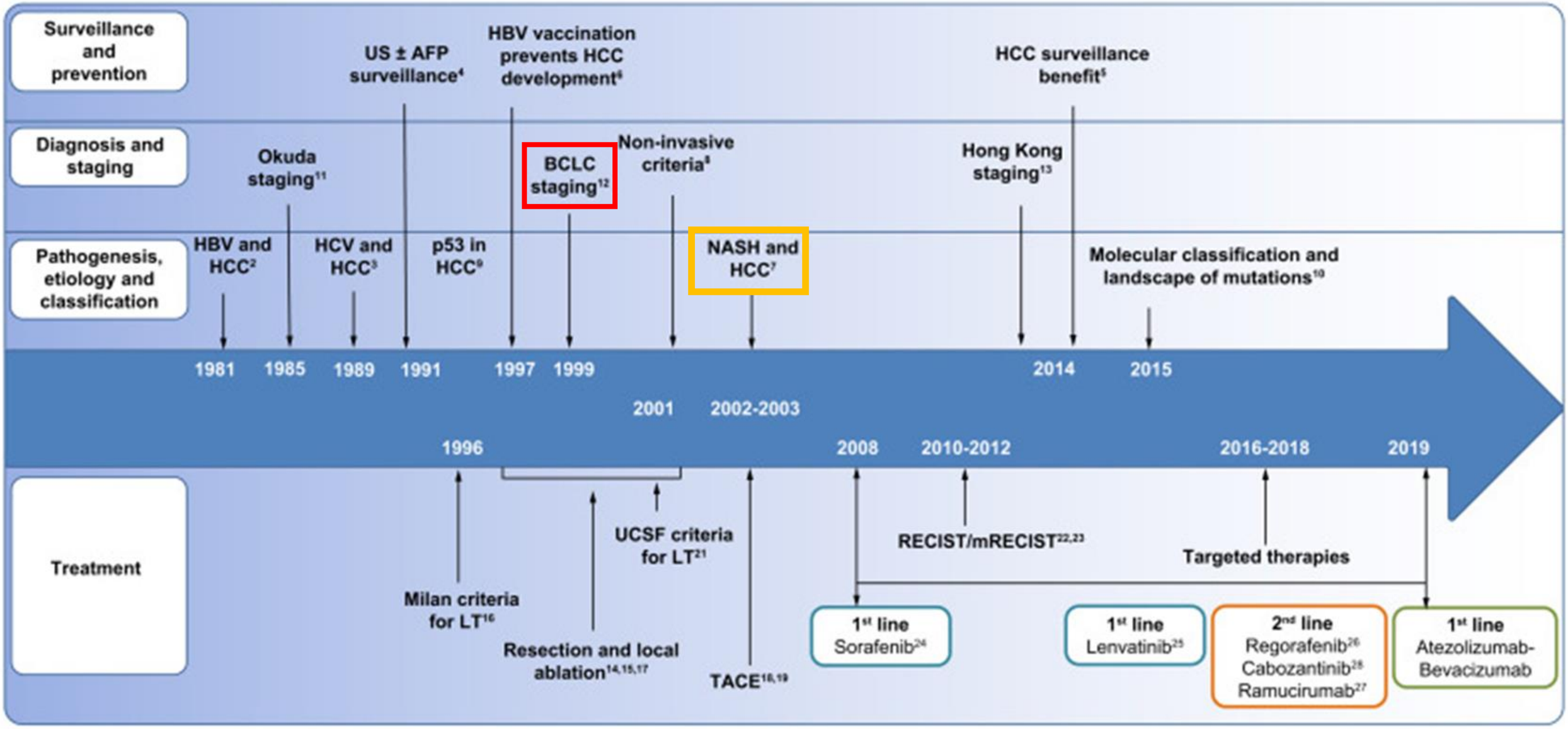


Table 3.2 Demographic characteristics of UK adult elective liver patients registered between 1 April 2020 and 31 March 2021

		Birmingham N (%)	Cambridge N (%)	Edinburgh N (%)	King's college N (%)	Leeds N (%)	Newcastle N (%)	Royal Free N (%)	Total N (%)
Number		**216**	**102**	**66**	**203**	**122**	**47**	**111**	**867**
Recipient sex	Male	132 (61)	67 (66)	43 (65)	132 (65)	81 (66)	34 (72)	81 (73)	**570 (66)**
	Female	84 (39)	35 (34)	23 (35)	71 (35)	41 (34)	13 (28)	30 (27)	**297 (34)**
Recipient ethnicity	White	186 (86)	95 (93)	60 (91)	171 (84)	111 (91)	42 (89)	80 (72)	**745 (86)**
	Non-white	30 (14)	7 (7)	6 (9)	32 (16)	11 (9)	5 (11)	31 (28)	**122 (14)**
Indication	Cancer	40 (19)	15 (15)	13 (20)	27 (13)	31 (25)	10 (21)	22 (20)	**158 (18)**
	Hepatitis C	6 (3)	4 (4)	1 (2)	3 (1)	2 (2)	0 (0)	3 (3)	**19 (2)**
	Alcoholic liver disease	52 (24)	22 (22)	20 (30)	69 (34)	39 (32)	12 (26)	27 (24)	**241 (28)**
	Hepatitis B	4 (2)	0 (0)	1 (2)	2 (1)	2 (2)	1 (2)	2 (2)	**12 (1)**
	Primary sclerosing cholangitis	25 (12)	15 (15)	7 (11)	16 (8)	15 (12)	8 (17)	17 (15)	**103 (12)**
	Autoimmune and cryptogenic disease	19 (9)	4 (4)	4 (6)	14 (7)	5 (4)	5 (11)	7 (6)	**58 (7)**
	Primary biliary cholangitis	17 (8)	8 (8)	8 (12)	15 (7)	7 (6)	3 (6)	5 (5)	**63 (7)**
	Metabolic liver disease	19 (9)	16 (16)	7 (11)	17 (8)	7 (6)	4 (9)	14 (13)	**84 (10)**
	Other	19 (9)	13 (13)	5 (8)	28 (14)	7 (6)	4 (9)	12 (11)	**88 (10)**
	Acute hepatic failure	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (0)**
	Regraft	14 (6)	5 (5)	0 (0)	12 (6)	7 (6)	0 (0)	2 (2)	**40 (5)**
Recipient HCV	No	202 (94)	94 (92)	61 (92)	190 (94)	116 (95)	47 (100)	101 (91)	**811 (94)**
	Yes	14 (6)	8 (8)	5 (8)	13 (6)	6 (5)	0 (0)	10 (9)	**56 (6)**
Encephalopathy	Absence	152 (70)	65 (64)	50 (76)	117 (58)	94 (77)	33 (70)	76 (68)	**587 (68)**
	Presence	64 (30)	37 (35)	16 (24)	86 (42)	28 (23)	14 (30)	35 (32)	**280 (32)**
Renal support	No	214 (99)	100 (98)	65 (98)	190 (94)	120 (98)	46 (98)	110 (99)	**845 (97)**
	Yes	2 (1)	2 (2)	1 (2)	13 (6)	2 (2)	1 (2)	1 (1)	**22 (3)**
Previous abdominal surgery	No	162 (75)	76 (75)	54 (82)	146 (72)	97 (80)	41 (87)	79 (71)	**655 (76)**
	Yes	54 (25)	26 (25)	12 (18)	57 (28)	25 (20)	6 (13)	32 (29)	**211 (24)**
Recip age (years)	Median (IQR)	52 (39, 60)	56 (48, 62)	57 (49, 64)	55 (46, 61)	54 (43, 61)	56 (46, 61)	53 (46, 60)	**55 (44, 61)**

NHS England “liver heath check” pilots

Aim: to increase the early diagnosis of liver cancer

- Delivered through HCV ODNs (11 ODNs originally)
- Funding was available for ODNs to deliver community fibroscanning to identify individuals with cirrhosis and enrol them in HCC surveillance
- Networks used funding for fibroscan technicians, nursing and admin support and pathway development, vans, peer support etc
- ODNs to deliver >2000 additional fibroscans in the community targeting high risk individuals

Who and where were people targeted?

- Targeting new individuals with:
  - More than 10 years of excess alcohol consumption
  - Suspected/known Alcohol Related Liver Disease (ARLD)
  - Suspected/known Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)
  - Current/previous Hepatitis B or C
- Fibroscans in the community
  - Drug and alcohol services
  - Homeless shelters
  - Primary care
  - Diabetes clinics
  - Prisons
  - Community vans

Results so far

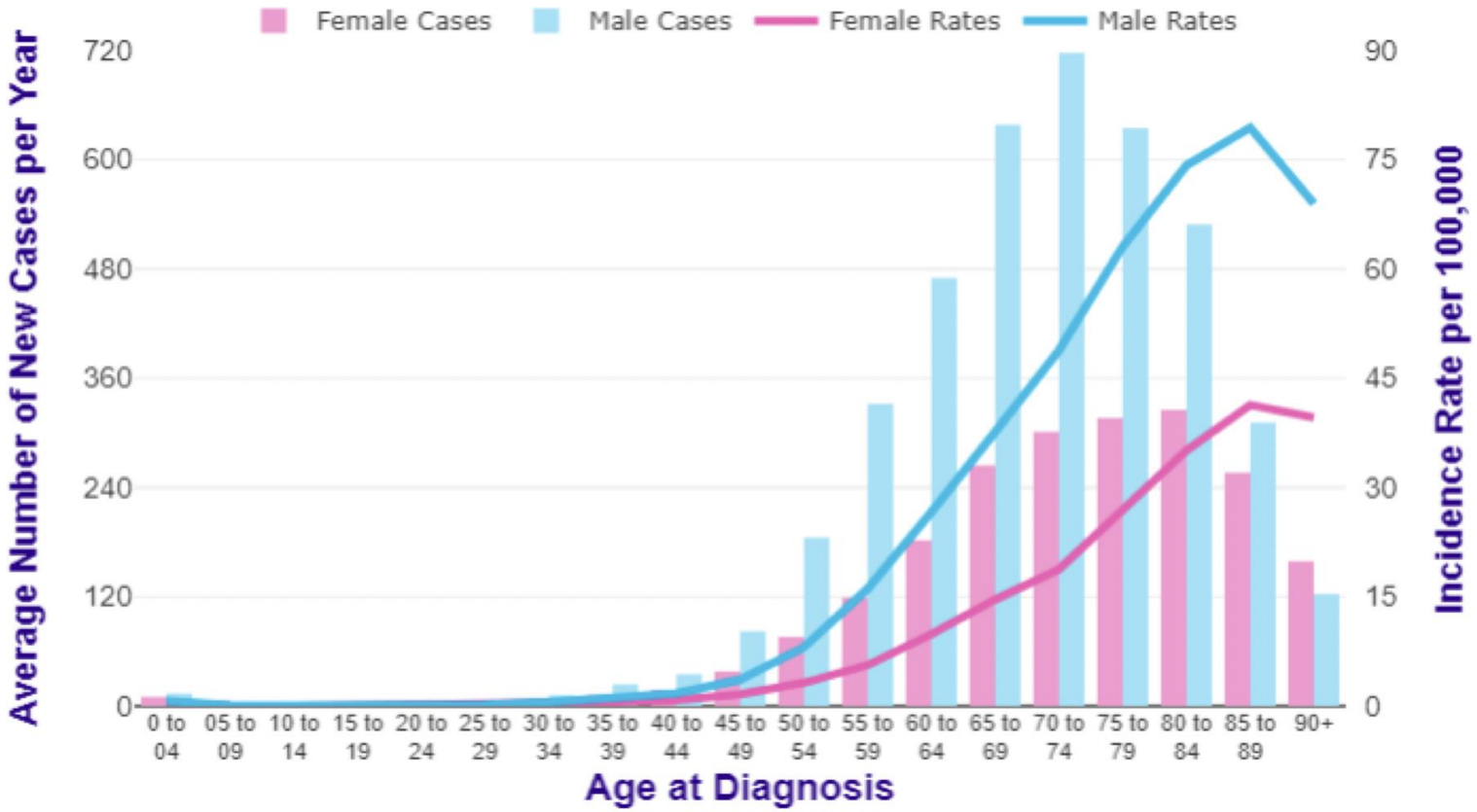
- >40,000 people had fibroscan so far across England
  - Harmful alcohol consumption
  - Type 2 diabetes
  - Obesity
  - Viral hepatitis
- 9% had Fibroscan >11.5 kPa

North East and North Cumbria

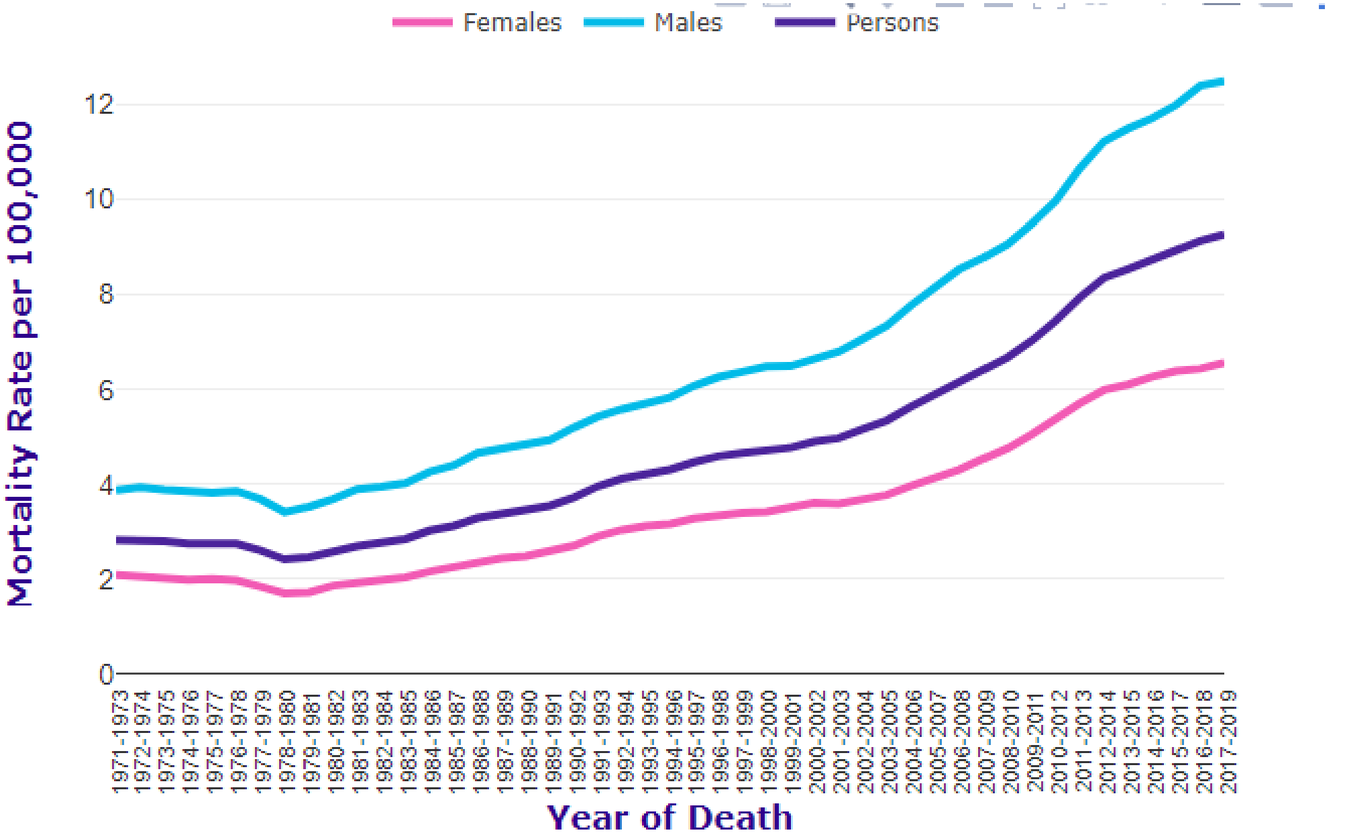
- 2410 fibroscans
- 210 (8% >11.5 kPa)
- Of 110 who have completed investigations
  - 43 cirrhosis
  - 51 advanced fibrosis
  - **4 HCCs**

HCC in numbers

- Over 6500 new cases annually in UK
- 5800 annual deaths in UK
- 20% diagnosed at early stage
- 30-40% 1 year overall survival
- 13% 5-year survival, 8% 10-year survival
- 80-90% will have underlying cirrhosis



Average number of new cases of liver cancer per year and age-specific incidence rates per 100,000 population, UK from 2016 to 2018.[9]


Females
Males
Persons
Mortality Rate per 100,000
0
2
4
6
8
10
12
1971-1973
1972-1974
1973-1975
1974-1976
1975-1977
1976-1978
1977-1979
1978-1980
1979-1981
1980-1982
1981-1983
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2008-2010
2009-2011
2010-2012
2011-2013
2012-2014
2013-2015
2014-2016
2015-2017
2016-2018
2017-2019
Year of Death


Female Excess Cases
Male Excess Cases
Female Rates
Male Rates
Average Number of Excess Cases per Year
Incidence Rate per 100,000
375
300
225
150
75
0
20
16
12
8
4
0
1
2
3
4
5
Deprivation Quintile

Challenges: Variations in care

A national survey of the provision of ultrasound surveillance for the detection of hepatocellular carcinoma

T J S Cross [1], A Villaneuva [2], S Shetty [3], E Wilkes [4], P Collins [5], A Adair [6], R L Jones [7], M R Foxton [8], T Meyer [9], N Stern [10], U Warshow [11], N Khan [12], M Prince [13], S Khakoo [14], G J Alexander [15], S Khan [16], H Reeves [17], Aileen Marshall [18], R Williams [19]

- Provision of surveillance was poor overall
- Many hospitals lacking the necessary mechanisms to flag abnormal results
- Lack of standard data collection including number of patients with cirrhosis and how many were developing HCC
- Majority of new HCC cases diagnosed at an incurable late stage (60%)

GIRFT
GETTING IT RIGHT FIRST TIME

Gastroenterology

GIRFT Programme National Specialty Report

When should we do surveillance?

Earlier diagnosis must offer a survival benefit
    - Early stage HCC has 80% 1-year survival
- Enough numbers of cases or high enough risk
    - Thousands of cases a year and rising
    - Can target high risk groups
- Acceptable surveillance modality
    - Blood tests and USS generally acceptable
- Accurate surveillance modality

- Sensitivity ranges from 21%-89%!!
    - Average is probably around 50% for early stage HCC
    - Roughly 80% for any stage HCC
    - Combination AFP and USS slightly better performance for earlier detection
    - Cost effective

- Earlier diagnosis=longer survival

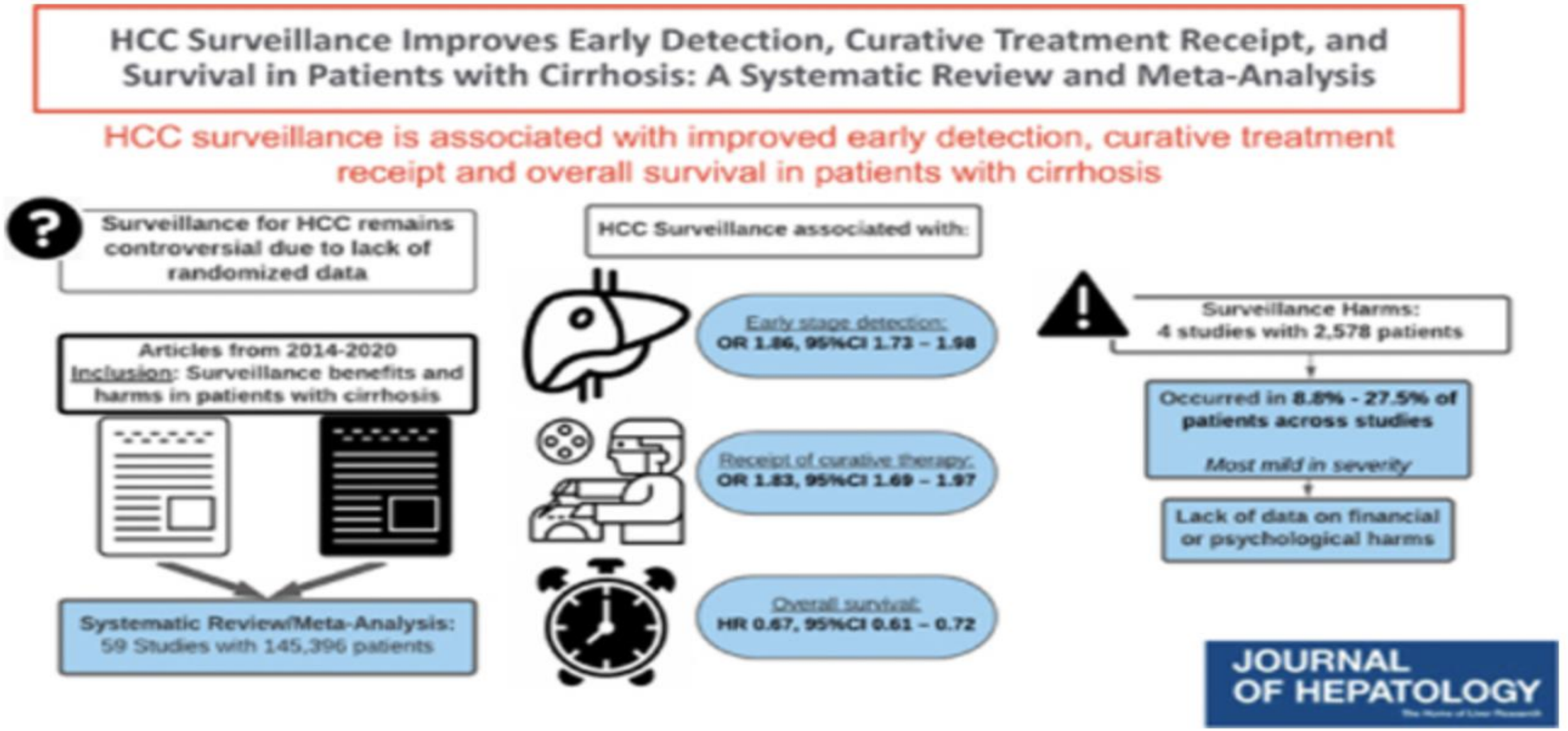
Patient population	Expected incidence per population	Threshold incidence for cost-effectiveness
Cirrhosis		
Hepatitis B cirrhosis	3–8% per year	0.2–1.5%
Hepatitis C cirrhosis	3–5% per year	1.5%
Alcohol-related cirrhosis	1.3–3% per year	1.5%
NASH cirrhosis	Unknown, estimated 1–2% per year	1.5%
Haemochromatosis	Unknown, estimated >1.5% per year	1.5%
α1-Antitrypsin deficiency	Unknown, estimated >1.5% per year	1.5%
Stage 4 primary PBC	3–5% per year	1.5%
Other cirrhosis	Unknown	1.5%
Non-cirrhotic hepatitis B		
Asian male hepatitis B carriers aged >40 years	0.4–0.6% per year	0.2%
Asian female hepatitis B carriers aged >50 years	0.4–0.6% per year	0.2%
Hepatitis B carrier with family history of HCC	Incidence higher than in those without family history	0.2%
African Black people with Heaptitis B	HCC occurs at younger age	0.2%
Patients with sufficient risk by risk score such as Page-B	>3% 5-year incidence if score >10	0.2%

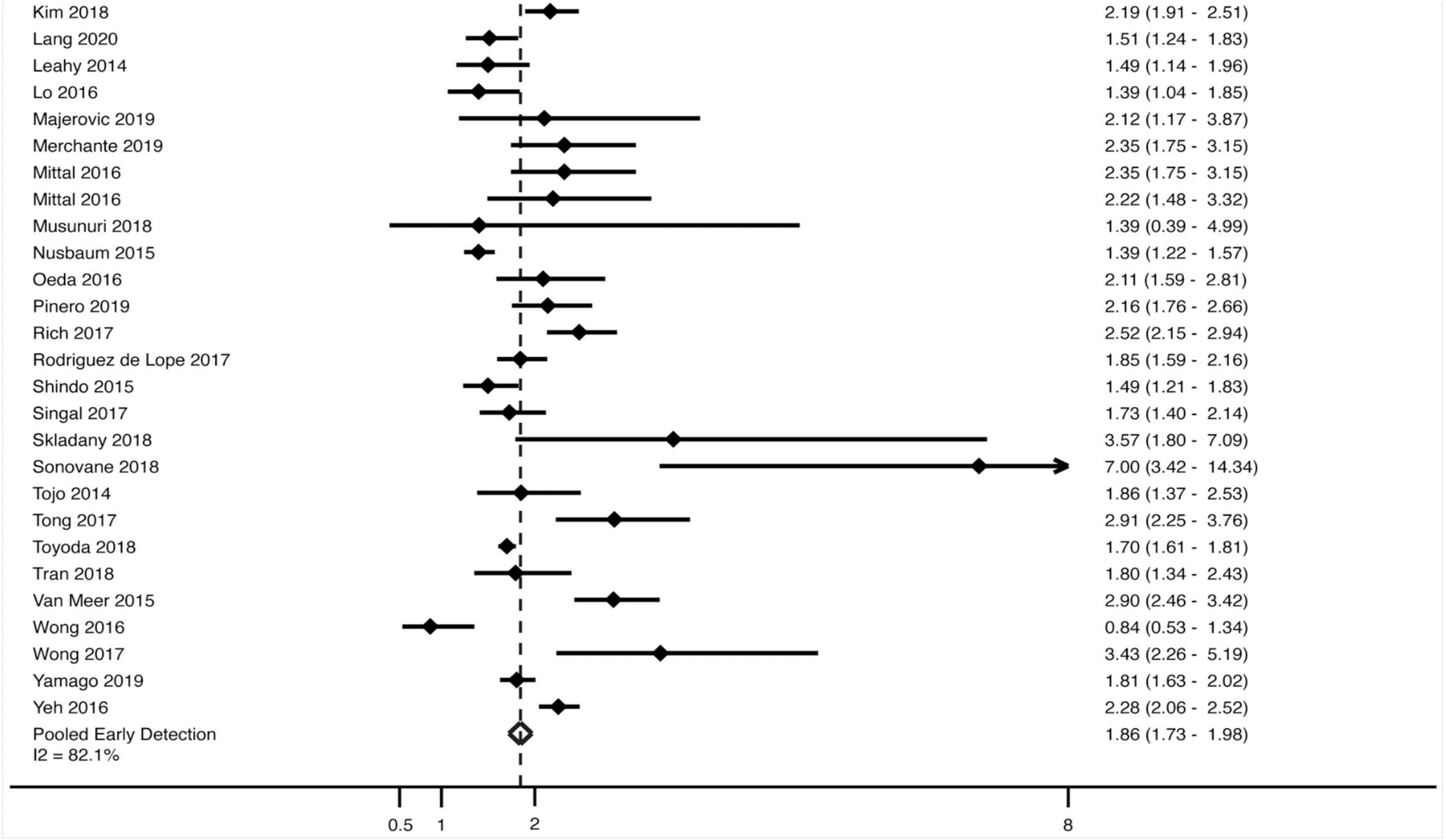
HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis ; PBC, primary biliary cholangitis.

Evidence of benefits of Surveillance?

- Initial conclusions derived from two large trials
  - BUT trials done in the far East- different aetiology and different population
  - 1997 trial in Shanghai- 35-55 aged HBV patients randomized to no surveillance vs 6/12 USS and AFP
  - Twice as many HCCs detected 75% underwent resection (80% 1 year surveillance) vs no curative treatment in other group (all died within 1 year)
  - 2003 Chinese trial- HBV men 3700 screened with AFP and then USS vs 1800
  - Earlier diagnosis/stage but no survival benefit at 5 years (better 1 and 3 year survival)
- A lot of data from retrospective studies
  - benefit of HCC outcome if in surveillance but may overestimate survival benefit
- Cost vs benefit analysis and risk cut offs
  - Risk above 1.5%
  - Largely cirrhotic patients

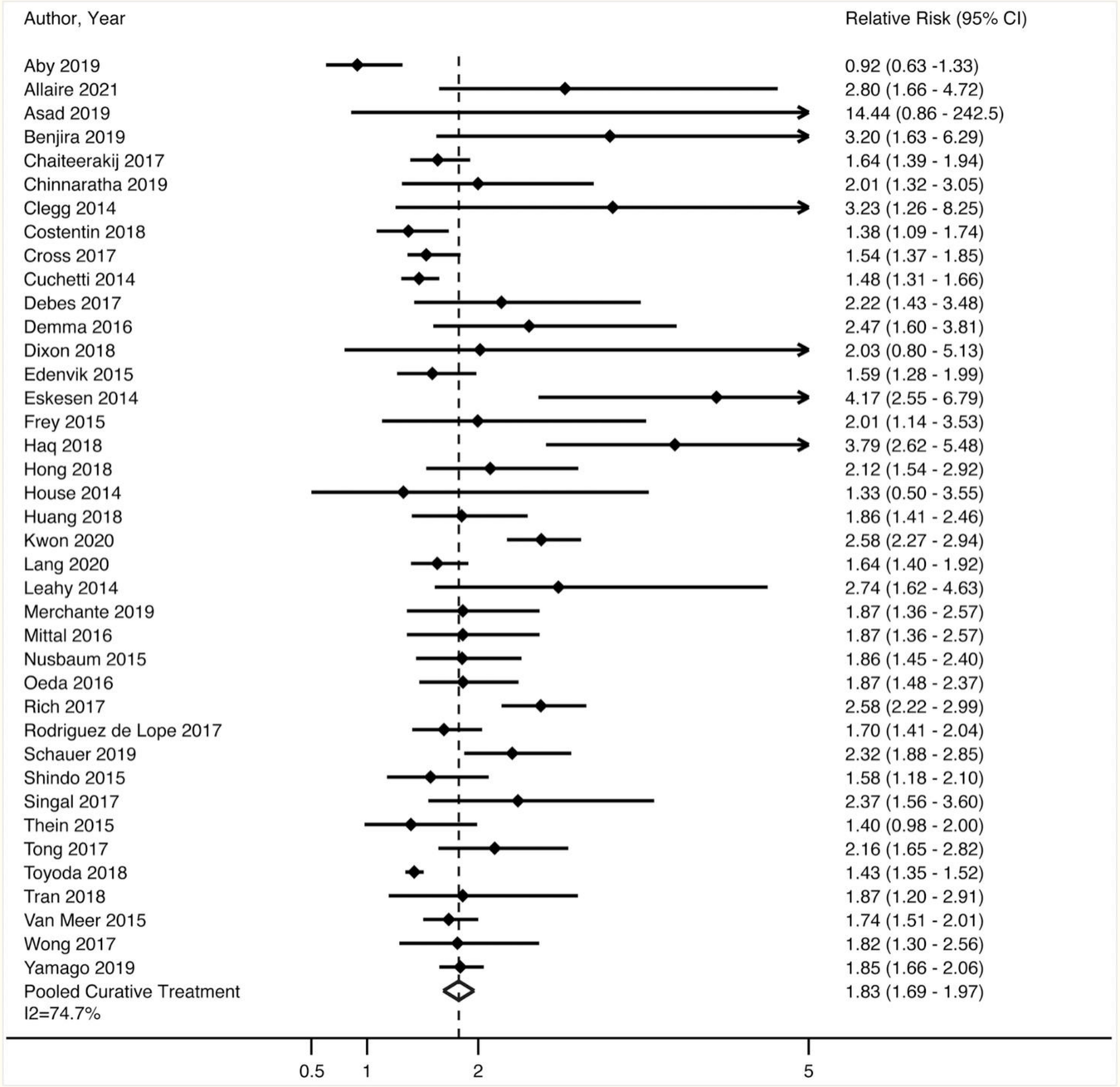
Singal et al. J Hepatol. 2022 Feb 6;77(1):128–139. doi: 10.1016/j.jhep.2022.01.023

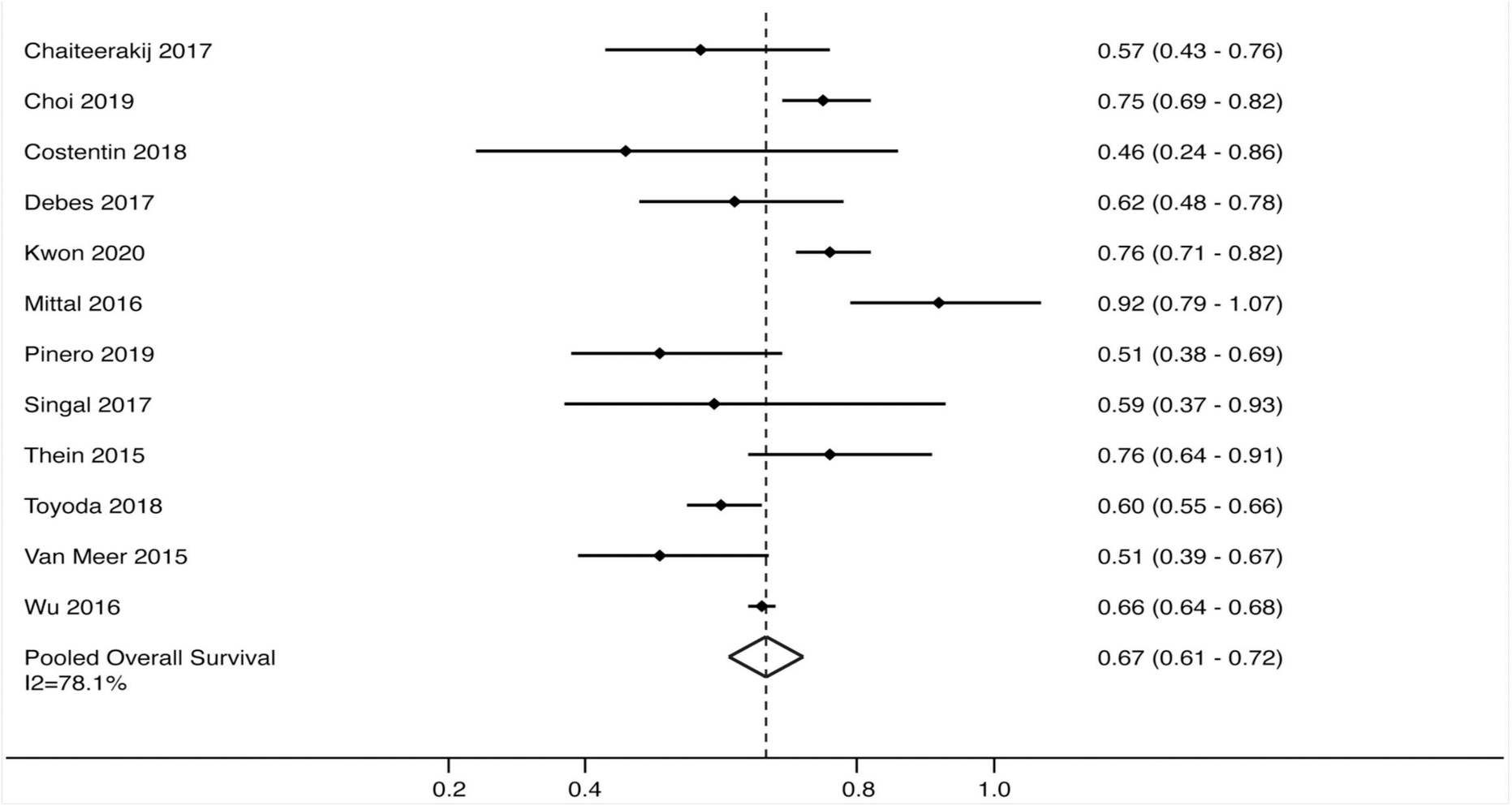




Patients who underwent surveillance were significantly more likely to have HCC diagnosed at an early stage (OR 1.94, 95% CI 1.80 – 2.08); however, there was significant heterogeneity (I^2=84%, p<0.001). DerSimonian and Laird method was used for a random effects model.

Figure 2. Association Between HCC Surveillance and Curative Treatment Receipt.





HCC surveillance was significantly associated with improved survival, with a pooled hazard ratio of 0.66 (95%CI 0.61 – 0.71); however, there was high heterogeneity (I^2=75%, p<0.001). DerSimonian and Laird method was used for a random effects model.

Challenges in surveillance

- Evidence not watertight but more than enough data to suggest surveillance could lead to earlier diagnosis and better outcomes
- There is no national HCC surveillance programme, so dependent on local practices and schemes to enroll and engage patients
- AFP not sensitive, so imaging is needed
- 1 in 5 HCC patients will have advanced cancer diagnosed despite being in a surveillance program
- There is a high false negative rate
  - LiRADS scoring systems of USS views

HCC surveillance, can we do better?

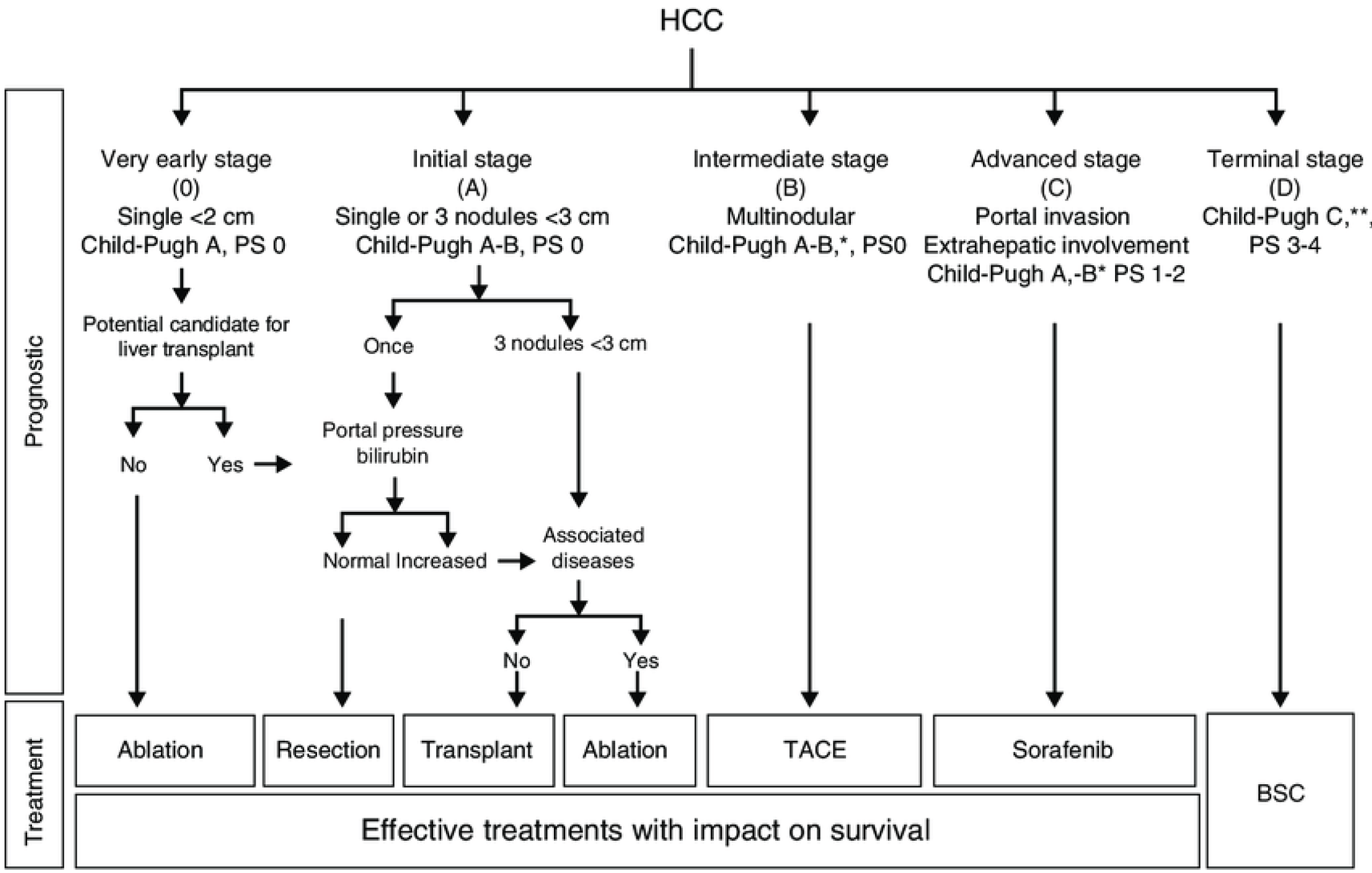
- Surveillance standards required
  - Ensuring all eligible patients enrolled
  - Timely review and action of reports
  - Appropriate engagement and support
  - Appropriate and timely review of results
- Should not be offered in decompensated patients or those with poor performance status
- Role for other modalities e.g. Abbreviated MRI.
  - A large study of MRI vs USS in 407 patients found sensitivity 82% vs 25%
  - More recent Korean study, slight improvement demonstrated with MR
- Small studies on role of CT- not much better for early stage HCC

'Risks of surveillance’

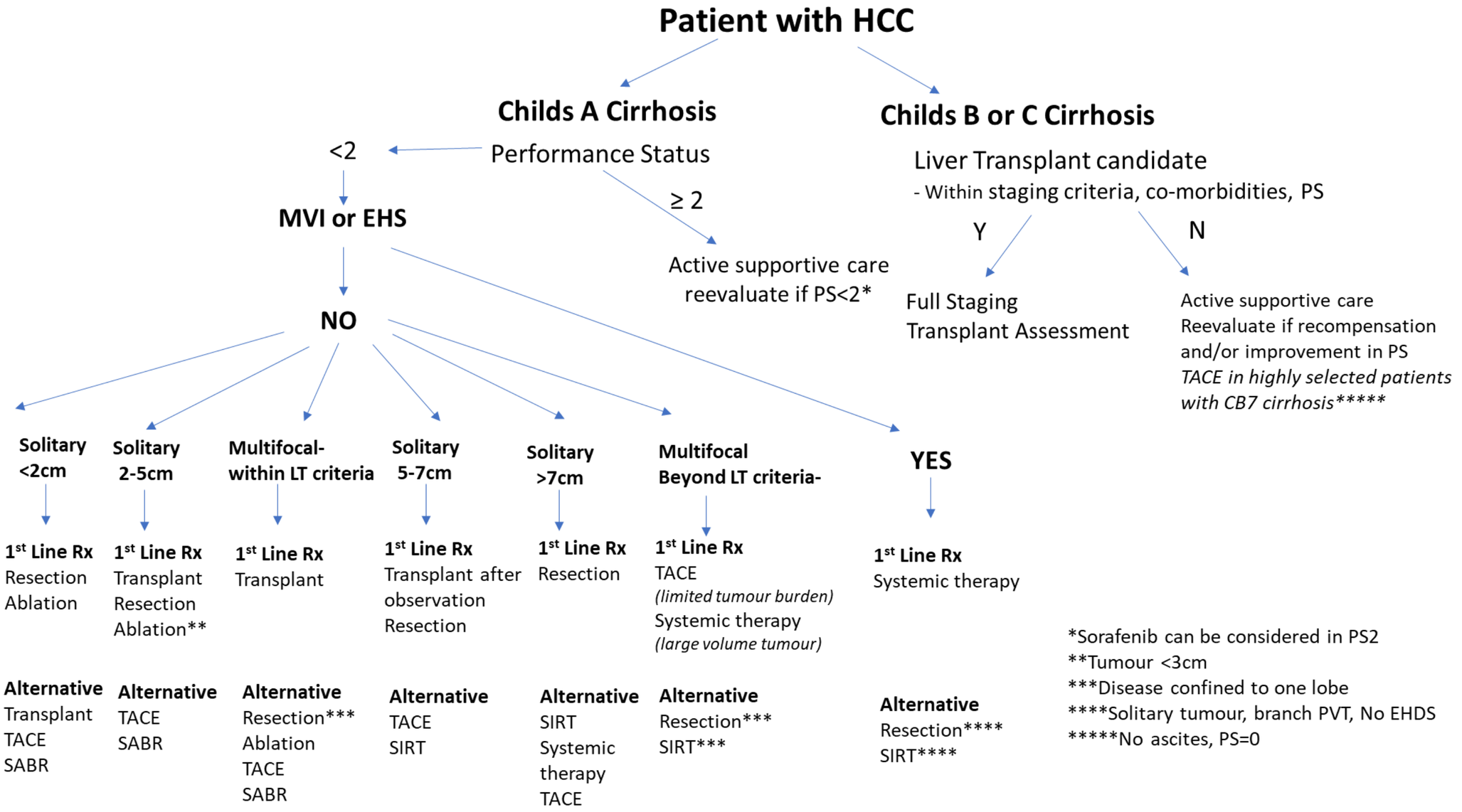
- False negatives
- False positives
- Patient acceptability and adherence
- Competing risks
  - Patient frailty
- Potential harms

HCC management

- An evolving paradigm shift


HCC
Prognostic
Very early stage
(0)
Single <2 cm
Child-Pugh A, PS 0
Initial stage
(A)
Single or 3 nodules <3 cm
Child-Pugh A-B, PS 0
Intermediate stage
(B)
Multinodular
Child-Pugh A-B,*, PS0
Advanced stage
(C)
Portal invasion
Extrahepatic involvement
Child-Pugh A,-B* PS 1-2
Terminal stage
(D)
Child-Pugh C,**,
PS 3-4
Potential candidate for liver transplant
No
Yes
Once
3 nodules <3 cm
Portal pressure bilirubin
Normal Increased
Associated diseases
No
Yes
Treatment
Ablation
Resection
Transplant
Ablation
TACE
Sorafenib
BSC
Effective treatments with impact on survival

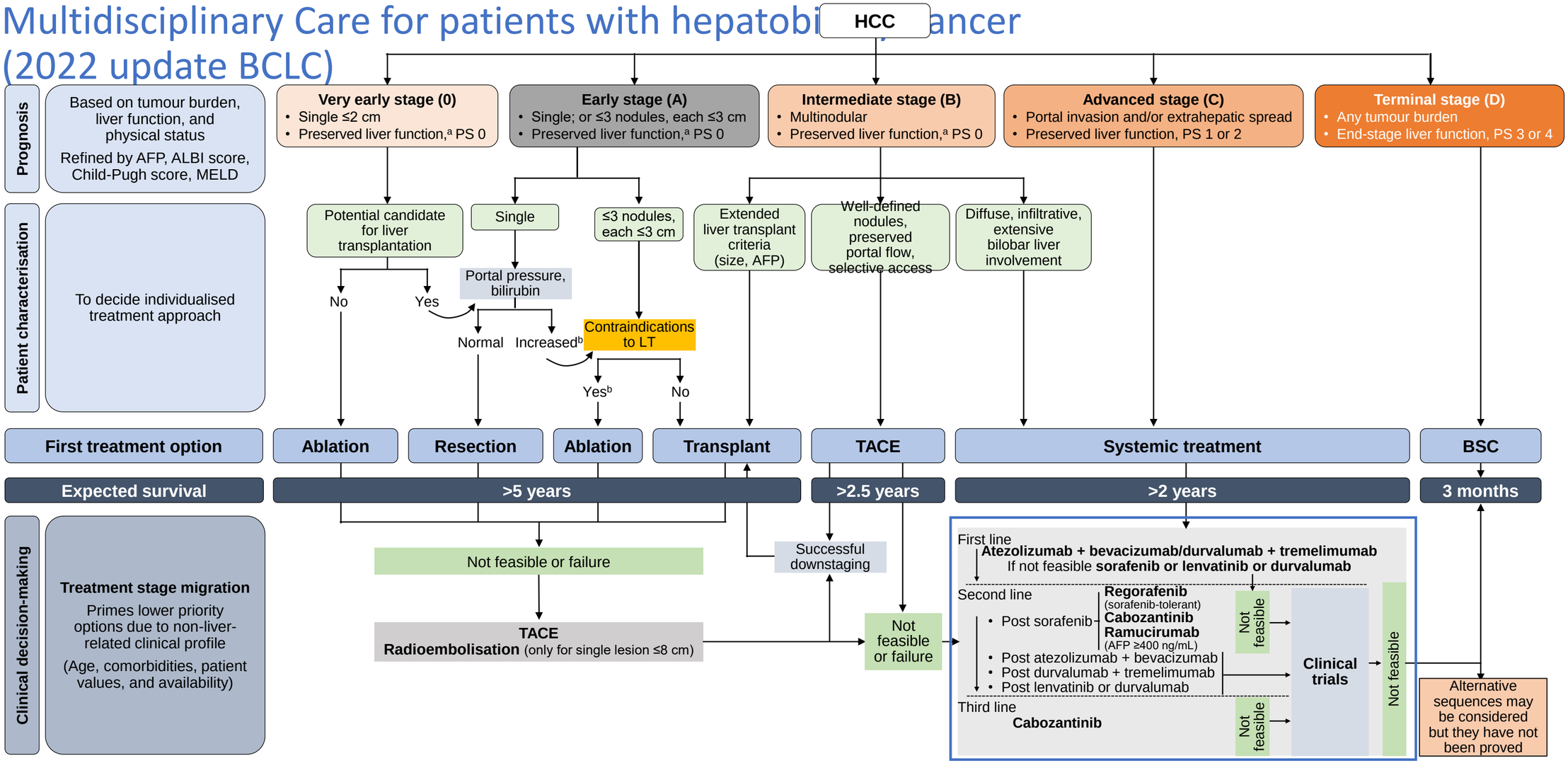
UK Guideline 2024



Suddle, Reeves et al Gut 2024 https://doi.org/10.1136/gutjnl-2023-331695

The place of IO IN THE TREATMENT LANDSCAPE

Multidisciplinary Care for patients with hepatobi[illegible]ancer (2022 update BCLC)



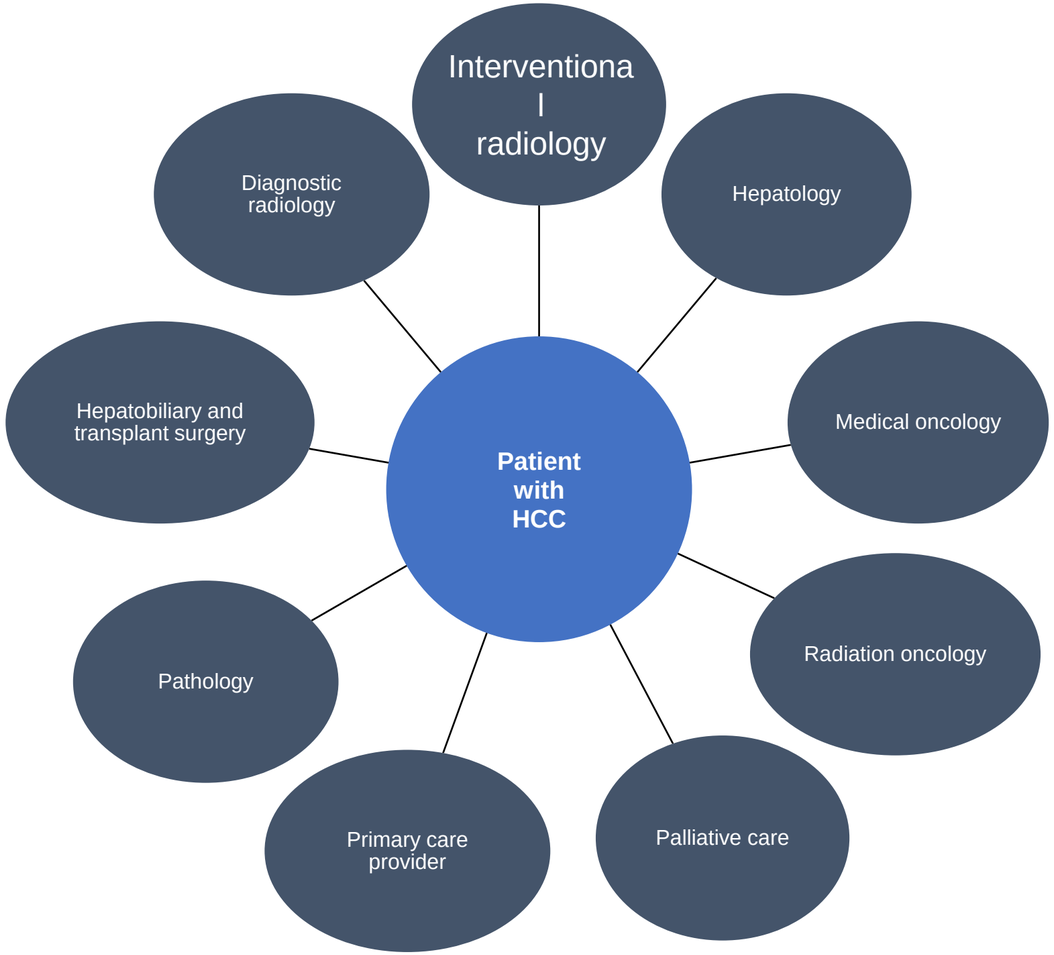
[a] Except for those with tumour burden acceptable for transplant; [b] Resection may be considered for single peripheral HCC with adequate remnant liver volume

AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model of end-stage liver disease; PS, performance status; TACE, transarterial chemoembolisation

Reig M, et al. J Hepatol. 2022;76:681-93

Multidisciplinary Team

Important to Determine the Course of Therapy for Patients with HCC



HCC, hepatocellular carcinoma

Conclusions

- Chronic liver disease and consequently HCC rates are rising
- National drive to improve early detection of liver disease will significantly increase workload
- Need sustained national improvement and equity in delivery of HCC surveillance
- Significant paradigm shift in the management of HCC over the past 5 years and ongoing evolution of care over the next 5-10 years
- Closer MDT working and collaboration will be essential in optimising treatment strategies and outcomes

Disclaimer

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