

Epidemiology and Diagnosis of HCC

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Disclosures

- Honoraria as a speaker:
 - BMS, MSD, Astrzeneca, Roche, Pfizer, Servier

HCC: Incidence

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- HCC is the sixth most common cancer and the fourth most common cause of cancer death worldwide

- Over 850,000 new cases of liver cancer (2018)
 - Eastern Asia: 570,000
 - Europe: 68,000
 - United States: 37,000

- Liver cancer is the leading cause of death in cirrhotic patients

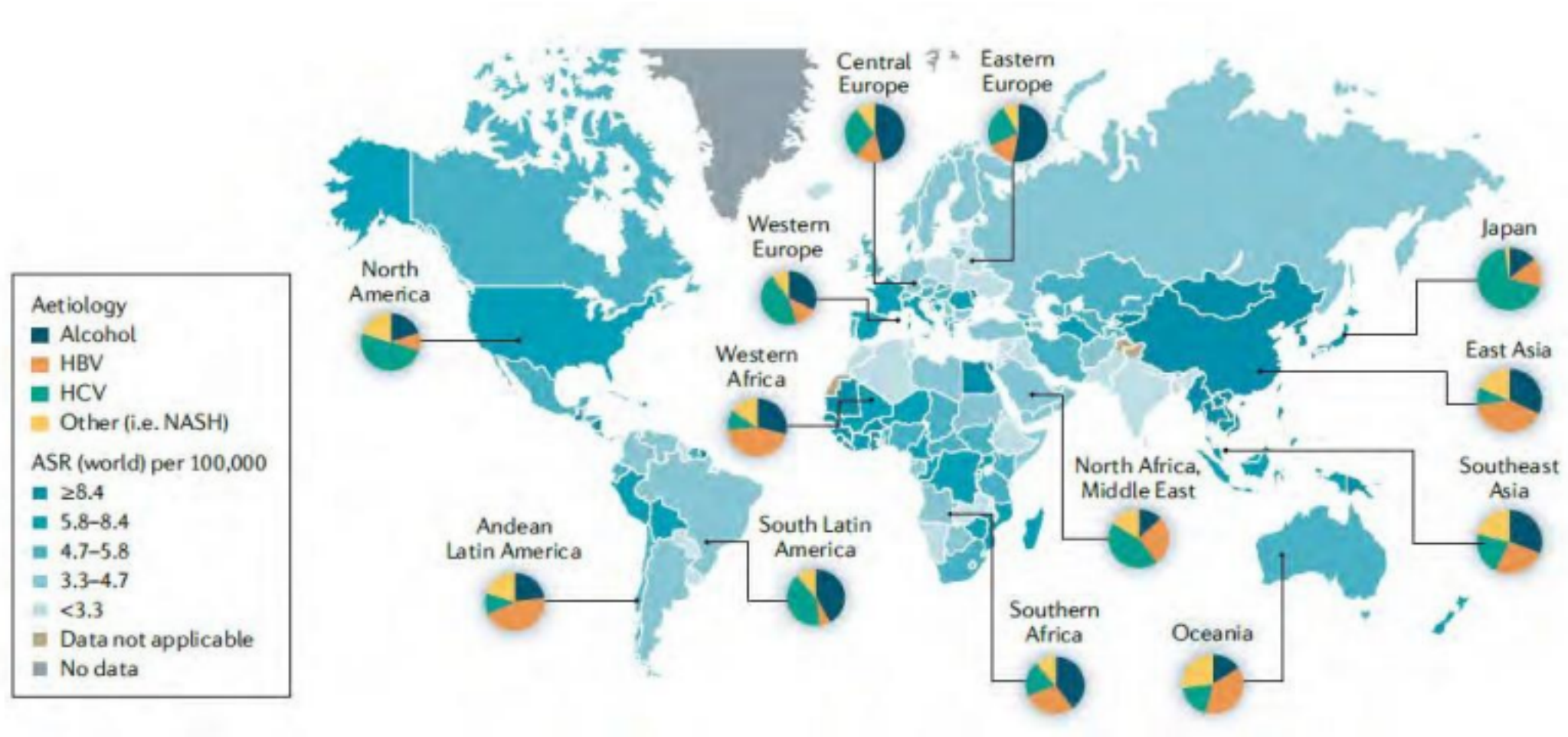
- The incidence of HCC is increasing globally and will reach 1M cases by 2025

Yang JD Nature Reviews GE 2019

World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France:
International Agency for Research on Cancer; 2020. Wild CP, Weiderpass E, Steward
BW, editors.

Incidence and risk factors-HCC

Incidence rates of HCC according to geographical area



Llovet

JM et al. Nat Rev DisPrimers 2021

Epidemiology and risk factors

- Incidence of HCC has been rising
 - Driven by increases in chronic viral infections and lifestyle-related risk factors
- **Cirrhosis is an important risk factor for HCC**
 - Up to 80% of HCC arises on a background of cirrhosis in the Western world¹
- Over the last 30 years, the etiological distribution of HCC in KSA has changed considerably: chronic HBV and HCV are now the most common etiologies, while NAFLD is emerging as an important etiology because of a rising incidence of obesity and metabolic risk factors.

The incidence of HCC is increasing worldwide; it is amongst the leading causes of cancer death globally		High
Chronic liver disease should be treated to avoid progression		High
		Strong

Alqahtani S, et al. Saudi J Gastroenterol 2020;26 (Suppl 1):S1-S40

1. Forner A, et al. Lancet 2018;391:1301–1314;

VISION رؤية
2030
المملكة العربية السعودية
KINGDOM OF SAUDI ARABIA



المجلس الصحي السعودي
Saudi Health Council

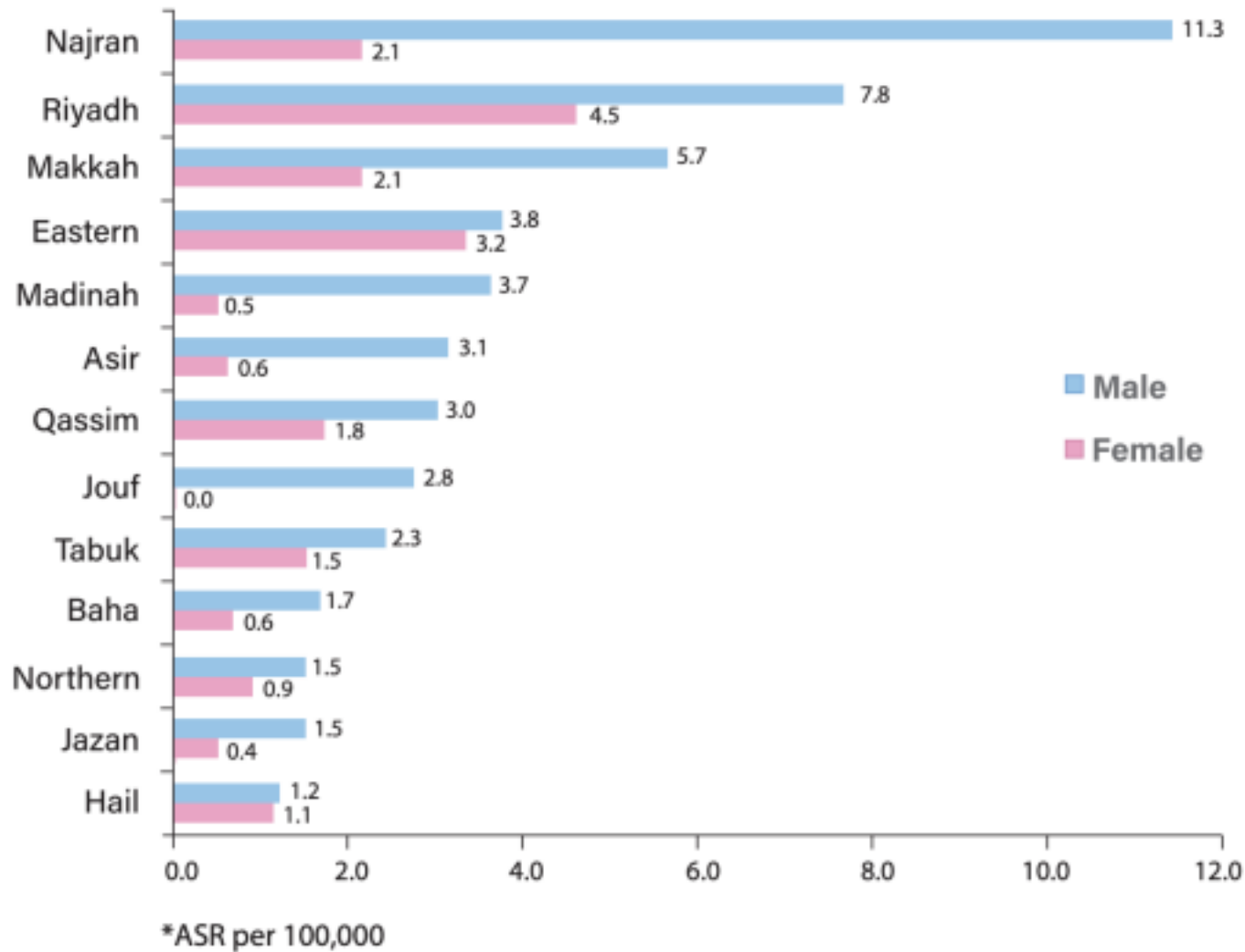
Saudi Health Council
National Cancer Center
Saudi Cancer Registry

Cancer Incidence Report
In Kingdom of Saudi Arabia
2018

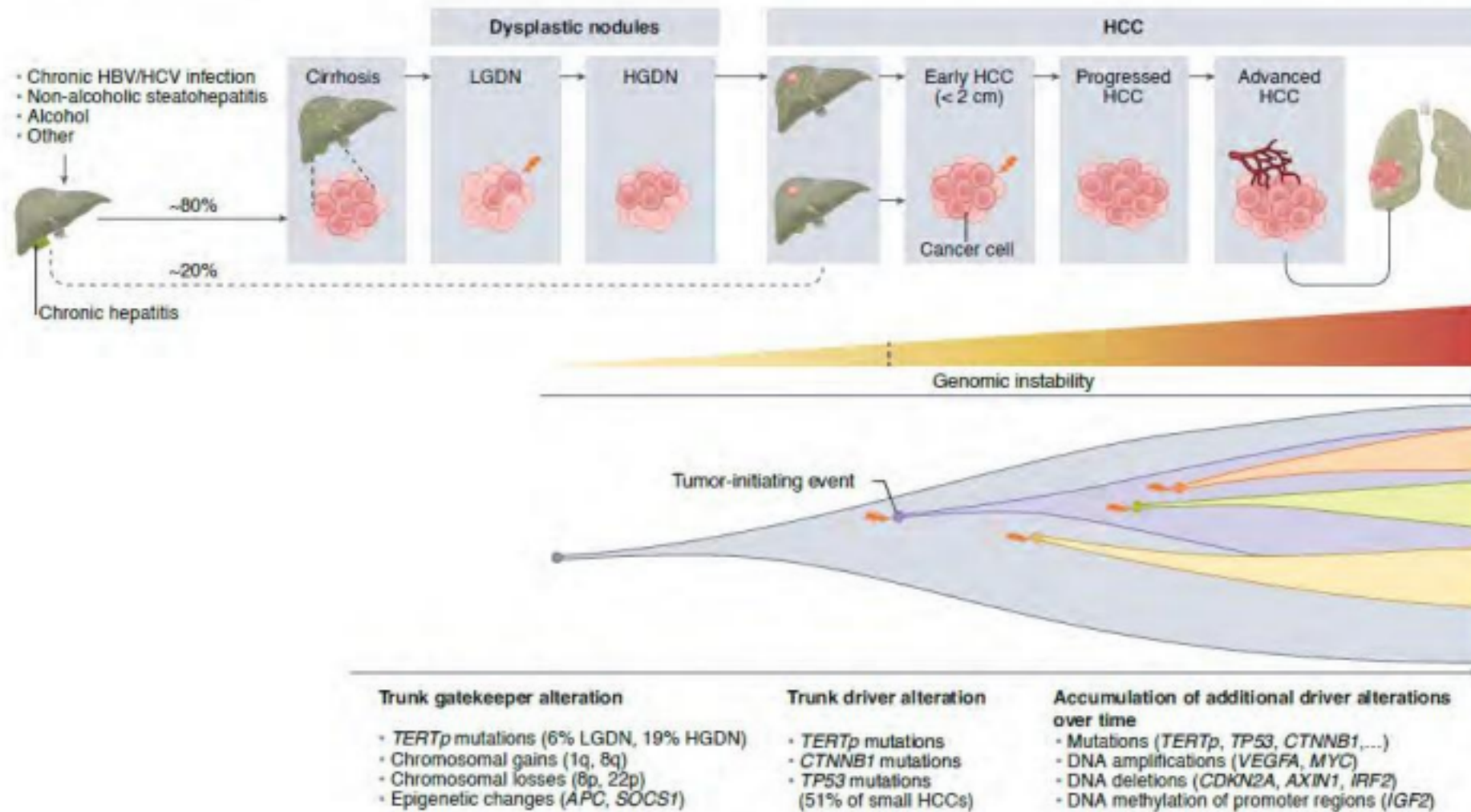
Table 2.7.3: Top ten cancers reported among Saudi adults by gender, 2018.

Male			Female		
	No	%		No	%
Colorectal	1044	16.3	Breast	2812	33.0
NHL	513	8.0	Thyroid	1037	12.2
Prostate	475	7.4	Colorectal	862	10.1
Bladder	386	6.0	Corpus Uteri	563	6.6
Lung	349	5.5	NHL	357	4.2
Liver	322	5.0	Ovary	278	3.3
Leukaemia	305	4.8	Leukaemia	222	2.6
Hodgkin's lymphoma	289	4.5	Hodgkin's lymphoma	189	2.2
Thyroid	273	4.3	Cervix Uteri	176	2.1
Kidney	263	4.1	Lung	154	1.8

Figure 3.9.3: Regional distribution of liver cancer (ASR*) among Saudi nationals, 2018.



The hepatocarcinogenic
process



Llovet JM et al. Nat

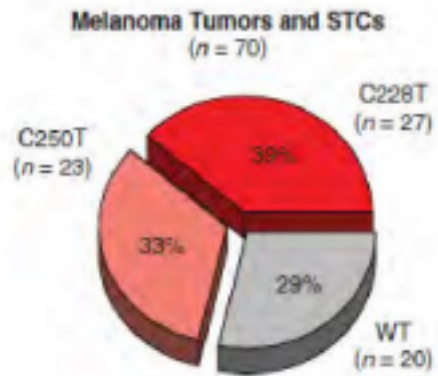
Cancer 2022

Pathogenesis of HCC

TERT promoter mutations

TERT promoter mutations- Melanoma (71%)

B

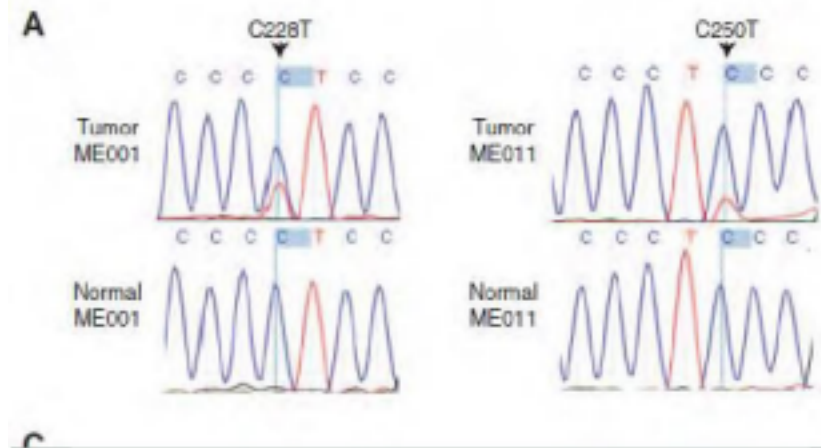


TERT promoter mutations

HCC (60%)

Dysplastic nodules (25%)

- HCC (60% +): Significantly associated to :
 - TERT over expression
 - non-HBV infection
 - CTNNB1 ($p < 0.0001$)
- Dysplastic nodules (25%+) associated to:
 - TERT overexpression
 - **First gatekeeper!!**

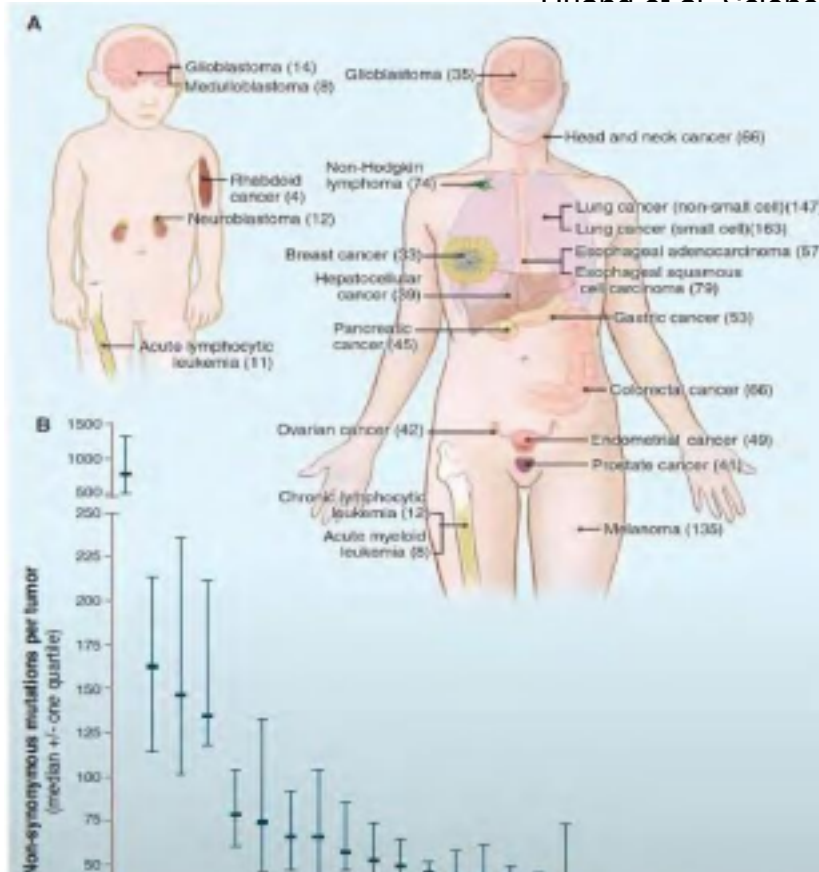


Nault et al, Nature communications 2013

Unger et al, Science 2013

Landscape of mutations in HCC

Genome sequencing in HCC(n=250)



SchulzeKet al, Nat Genetics2015

Undruggable
mutations

Vogelstein et al, Science2013

Risk factors

HBV

- HCC annual incidence of 0.42%
- NAs associated with risk reduction, but not elimination of HCC in patients with

CHB

HCV

- HCC annual incidence 0.5-10%, considerable (50%–80%) and steady HCC risk reduction over time of *de novo* HCC among pts achieving DAA-related SVR
- Absolute risk of HCC persisted in patients with DAA-induced SVR

Alcohol consumption

- Remains a significant risk factor, two- to three-fold lower risk of HCC than patients with cirrhosis due to viral hepatitis
- Significant increased risk of 4% per 10 g alcohol intake per day

Metabolic syndrome / NAFLD

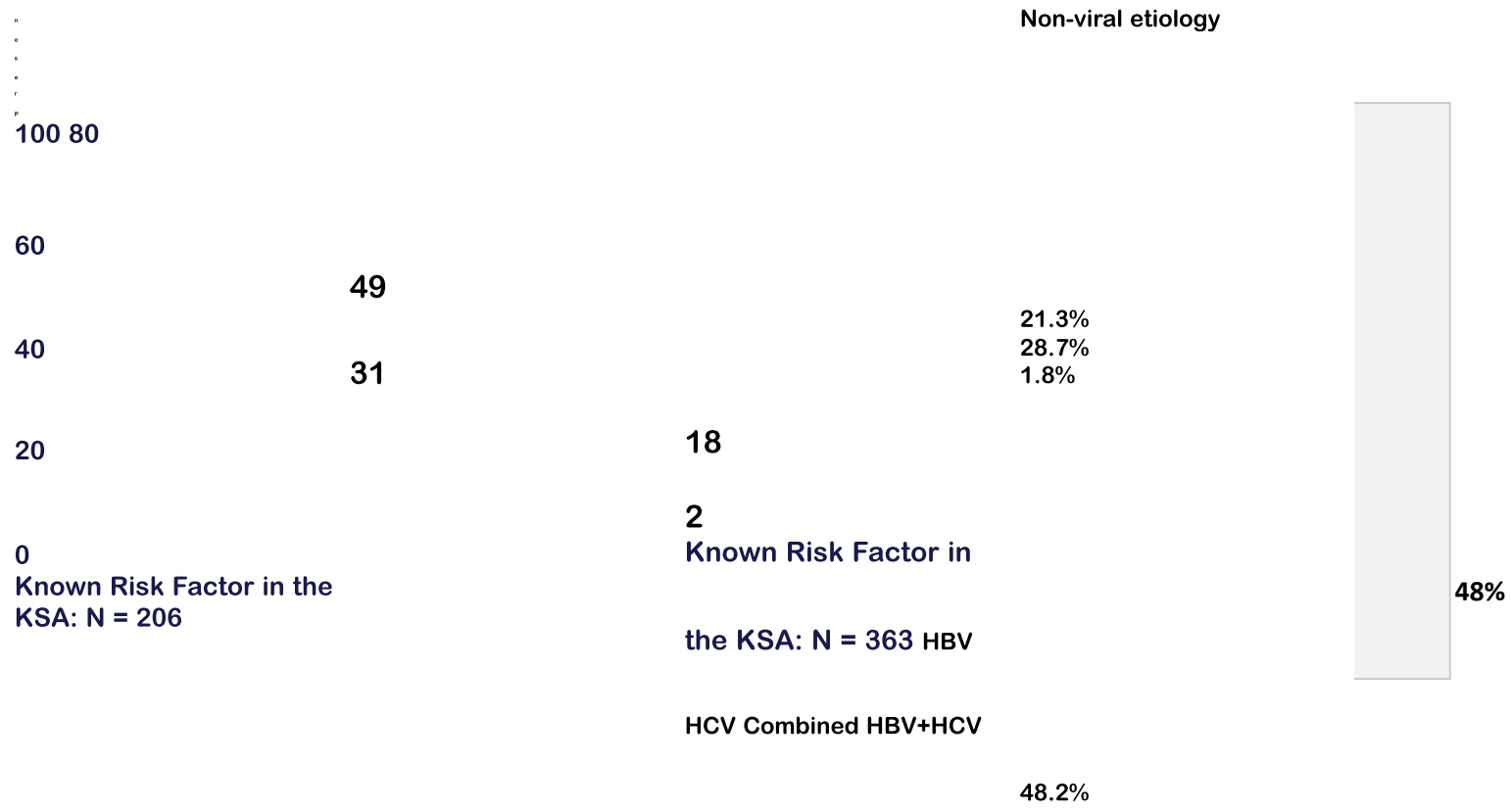
- The most common liver disease and a major risk factor for HCC in most developed countries
- Irrespective of NAFLD, obesity and diabetes increase HCC risk

Etiology of HCC in Saudi Arabia

Increasing Burden of NASH-related HCC

Two centers (KSUMC & PSMC), 2003 – 2008; and 2003 - 2012

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Alzanbagi A, et al. Saudi J Gastroenterol 2018;24:S1-S10

HBV + HCV
HBV HCV NASH
 Hepatitis C Hepatitis B Others

Sanai FM, et al. Dig Dis Sci 2010;55:3568-75.
 Alswat K, et al. Hepat Mon 2013;13(5):e7612

Successful vaccination programmes have had a significant effect
 on HBV prevalence

in Saudi children 6.70%

10% 8% 6% 4% 2%

Decline in HBsAg-positivity

0%

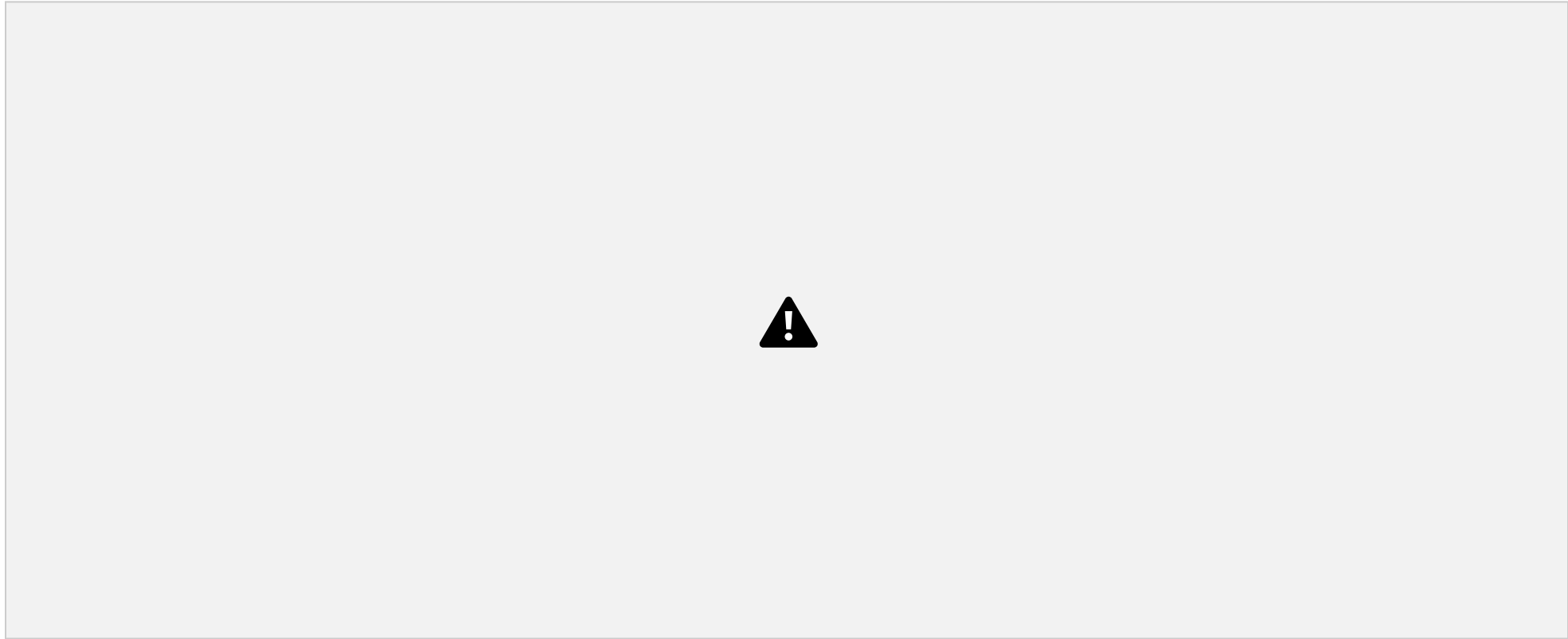
0% 0.16% 0%

1989 1992 1997 2007/8

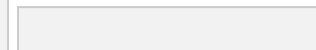
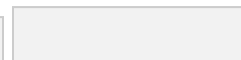
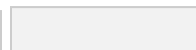
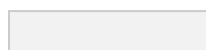
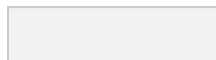
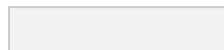
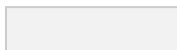
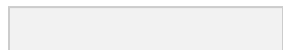
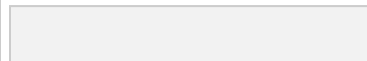
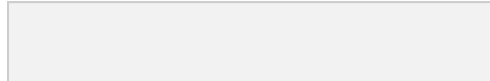
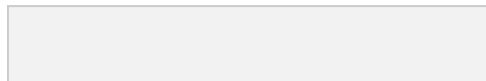
AlFaleh FZ, *et al.* J Infect 2008;57(5):404-9

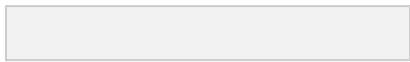
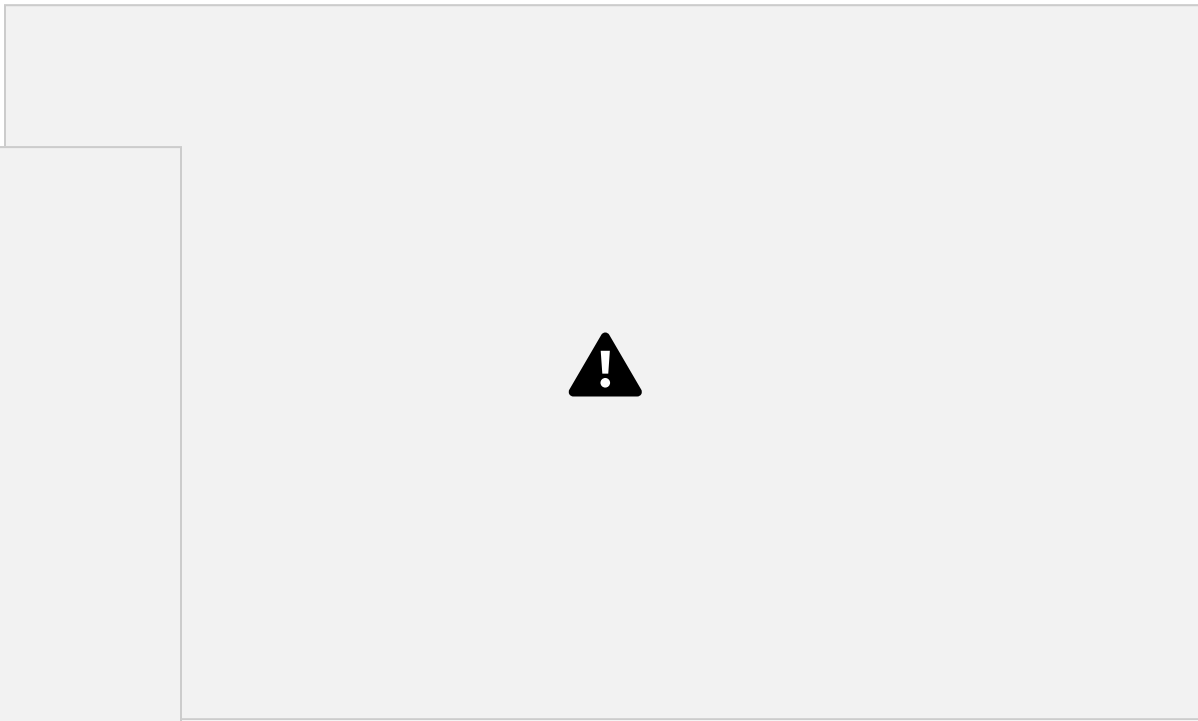
Incidence of HCC in patients with HCV-associated cirrhosis treated with direct-acting antiviral

agents



Calvaruso V, et al. Gastroenterology 2018;155:411-21.e4.





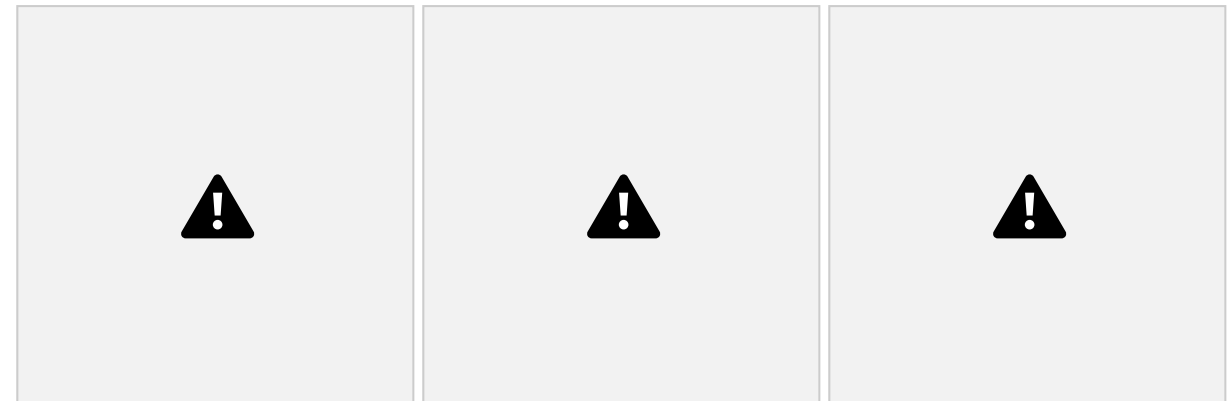
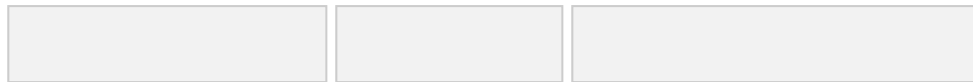
ScientificRegistryof Transplant
Recipients(2002-2016)

x11.5

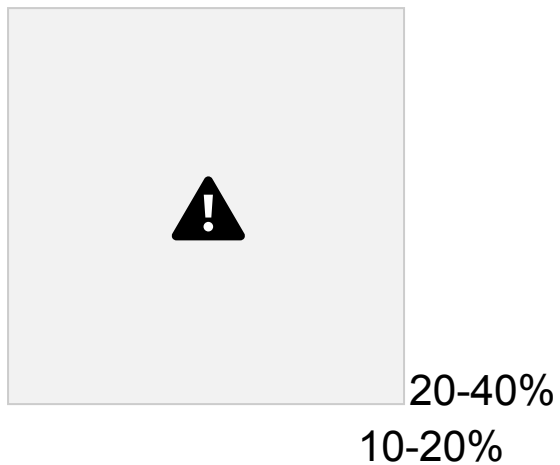
x6.2

Younossi Z Clinical Gastro-Enterology 2018

Younossi Z Hepatology 2018



hepatitis/NASH Steato
Steatosis/NAFLD Cirrhosis HCC



Annual incidence
2.4-12%

➤ Absence of cirrhosis (up to 40%)

- Transformation to pre-existing Hepatocellular adenoma
- Larger tumors, well-differentiated

Paradis V et al Hepatology 2009, Dyson J J Hep 2014, Mittal S Clin Gastroenterol Hepatol 2016, Than NN QJM 2017



➤ Older patients

Absence of Cirrhosis in Subjects with NAFLD Associated HCC – Meta-analysis

- Meta-analysis of 30 studies including

13,371 subjects with NAFLD-associated HCC.

- NAFLD-HCC in non-cirrhotic individuals occurs more frequently in Asians vs. Europeans or North Americans.
- NAFLD-HCC tends to be more advanced at diagnosis.
- NAFLD-HCC occurs in 37% of non-cirrhotic individuals, and is more frequent in non-cirrhotic livers than in non-NAFLD-HCC.

Castellano M, et al. J Clin Med; 2021;10(20):4638

Molecular differences between NASH-HCC and non- NASH-HCC

NASH-HCC Non-NASH-HCC



Obesity, diabetes, metabolic syndrome.

~10% of HCCs globally
~20% in Western countries

Male : female ratio = 1.2:1

↑ *ACVR2A* and *TP53*

mutations ↑

MutSig-NASH-HCC

↑ Wnt/TGF-β proliferation

SNPs in *PNPLA3*, *TM6SF2*,
MBOAT7 and *GCKR*

Activation of dysfunctional immune +++ cells including CD8 PD1 cells, IgA plasma cells, NK cells, and T_H17 cells that disrupt tumour immune surveillance

HBV infection, HCV infection, alcohol.

~90% of HCCs globally
~80% in Western countries

Male : female ratio = 2-3:1

↑ MutSig24

↓ Wnt/TGF-β proliferation

SNPs in *GTSM1* and *GSTT1*

ASH: Increased M2
macrophages and gMDSC
infiltration

HBV: Exhaustion of effector
CD8+ T cells and infiltration
of
immunosuppressive T and B
cells

HCV: CD8+ T cell exhaustion
and immune evasion by
interference with
MHC1-dependent antigen

presentation

Pfisteret al., Nature2021

↓ Underlying cirrhosis (~65%) ↑ Underlying cirrhosis (> 80%)

↑ oxidative DNA damage, microbial

signals generated by gut bacterial

metabolism

Necroinflammation from chronic hepatitis
viral exposure

Llovet JM et al, Nature ReviewsGastroenterology & Hepatology (submitted)

Diagnosis work-up

Based on histological analysis and/or contrast enhanced imaging findings

Risk factors for chronic liver disease

- IV drug abuse
- alcohol intake
- metabolic syndrome (obesity, diabetes, hypertension)

Symptoms and signs of chronic liver disease

PS (distinguish cancer-related symptoms from those of liver failure with cirrhosis) and nutritional status

Aetiology of liver disease: HBV (antibody status), autoimmune disease

Liver function: Prothrombin, albumin

Complete blood cell count including platelets

Tumour marker: SerumAFP

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Based on histological analysis and/or contrast enhanced imaging findings

Upper endoscopy: Varices and/or portal hypertensive gastropathy

Optional: Transjugular measurement of portal pressure

Diagnosis work-up

Liver dynamic (multiple ph liver (number and size of
CEUS can also be used fo not considered appropriat
CT of the chest, abdomen
Useful for nodules with no

Required to diagnose HCC in non-
Should be carried out according to centre based innovative treatment
Ideally, should evaluate tumour an

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Diagnosis and pathology / Molecular biology

Diagnosis requires identification by multiphasic contrast-enhanced CT or MRI of typical vascular hallmarks of HCC in a nodule of > 1 cm diameter
Multiphasic MRI is more sensitive than multiple detector CT
MRI with diffusion-weighted imaging and hepatobiliary contrast agents may identify high-risk nodules
Histopathological diagnosis of tumour biopsies relies on H&E staining and may be supplemented with IHC, which is also recommended in unclear cases

Significant CK19 expression indicates a poor prognosis

In highly differentiated HCC, additional histological and cytological criteria can support the diagnosis and additional IHC markers can improve diagnosis

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Staging and risk assessment

Staging should be conducted according to the BCLC system and includes:

- Assessment of tumour extent
- AFP level
- Liver function
- Portal pressure
- Clinical PS

Contrast-enhanced MRI or helical CT are recommended to evaluate tumour extent FDG-PET scanning is not recommended

Liver function is assessed by the Child–Pugh scoring system and the ALBI score can distinguish between good and poor-prognosis patients

Oesophageal varices and/or splenomegaly with blood platelet counts of 100×10^9 cells/L suggest clinically important portal hypertension

SASLT Guidelines Diagnosis Algorithm for HCC

Prevention of HCC

- Primary prevention of HCC can be achieved with universal vaccination against HBV
- Progression to cirrhosis and HCC can be prevented by:
 - Antiviral treatment in patients with chronic hepatitis B and C*
 - Adoption of healthy lifestyle measures

Vaccination against hepatitis B reduces the risk of HCC and is **recommended for all newborns and**

high-risk groups High Strong

<p>In patients with chronic hepatitis, use antiviral therapies to:</p> <ul style="list-style-type: none"> • Maintain HBV suppression in chronic hepatitis B • Maintain SVR in chronic hepatitis C 	<p>High</p> <p>Strong</p>
<p>Once cirrhosis is established:</p> <ul style="list-style-type: none"> • Successful antiviral therapy reduces but does not eliminate the risk of HCC development Moderate 	

Alqahtani S, et al. Saudi J Gastroenterol 2020;26 (Suppl 1):S1-S40

Surveillance in patients at high risk of HCC

- Surveillance is recommended in specific target populations

<ul style="list-style-type: none"> • Cirrhotic patients, Child–Pugh stage A and B High Strong 	
<ul style="list-style-type: none"> • Cirrhotic patients, Child–Pugh stage C awaiting LT High 	<p>Strong</p>
<ul style="list-style-type: none"> • Non-cirrhotic HBV patients at intermediate or high risk of HCC (>45 years, advanced fibrosis, high viral load) <p style="text-align: center;">Low</p>	<p>Weak</p>
<ul style="list-style-type: none"> • Non-cirrhotic HCV patients with advanced (F3) fibrosis High 	<p>Strong</p>

- Interval should be dictated by rate of tumour growth and tumour incidence in target population
 - **6-month interval is reasonable and cost-effective**
 - **3 months:** no clinical benefit
 - **12 months:** fewer early stage diagnoses and shorter survival

Alqahtani S, et al. Saudi J Gastroenterol 2020;26 (Suppl 1):S1-S40

Uncertainties in surveillance strategy

- Benefit of surveillance has not been established in all risk groups
- US remains the method of choice
 - Serological tests are not currently cost-effective

Role of surveillance for patients with NAFLD without cirrhosis is unclear Low	
Surveillance should be performed by experienced personnel in all high-risk populations using abdominal US every 6 months Moderate	Strong
Tumour biomarkers for accurate early detection are still lacking* Low	-

Uptake of multidisciplinary management of HCC

In USA

- 44% of physicians routinely adopted a multidisciplinary approach •
- 38% discussed their patients at a multidisciplinary meeting only when they were uncertain about management strategy

In Europe

- 63% of physicians applied the multidisciplinary strategy of HCC

Multidisciplinary management of HCC improves access to therapy

Any treatment	228 (75)	212 (61)	0.0001
Radiofrequency ablation	114 (37)	47 (13)	<0.0001
Chemoembolisation	63 (21)	59 (17)	0.16
Radioembolisation	47 (15)	6 (2)	<0.0001
Multimodality locoregional therapy	38 (12)	8 (2)	0.004
Resection	32 (10)	57 (16)	0.02
Systemic chemotherapy	33 (11)	57 (16)	0.11
Liver transplantation	72 (24)	48 (14)	0.0001

Conclusions

- **Epidemiology**
 - Significant changes in risk factors
 - NAFLD as emerging cause worldwide (A new model of liver carcinogenesis: older patients, less cirrhosis, ...)
- **Pathology**
 - Moving from a classical pathology to a pathomolecular approach
 - Provide a comprehensive diagnostic, prognostic, and theranostic classifications
- **Prevention & screening**
 - Antiviral treatment in patients with chronic hepatitis B and C, healthy lifestyle measures
 - Screening for high-risk patients
- **Adoption of MDTB for the management of HCC**