Guilherme Macedo

MD, PhD, MACG, AGAF, FAASLD

WGO President

Director of Department of Gastroenterology

Centro Hospitalar Universitario S.João, Faculdade Medicina, Porto, Portugal

Director of WGO Gastroenterology&Hepatology Training Center Porto

WHY SHOULD WE CARE ABOUT HEPATOCELLULAR CARCINOMA IN NASH?

IFSO NAPOLI 2023

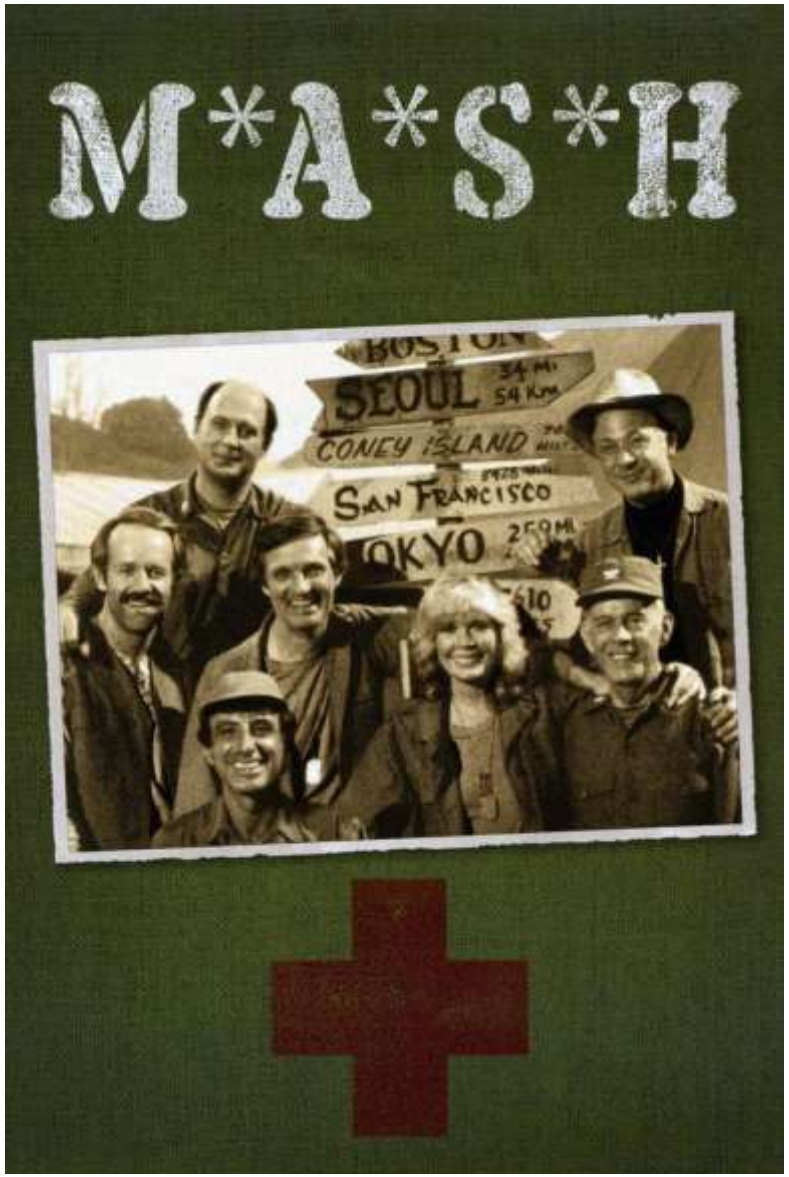
I have the following potential conflict(s) of interest to report:

- Receipt of honoraria or consultation fees: Abbvie, MSD, Gilead, Roche, Bayer
- Participation in a company sponsored speaker's bureau: Abbvie, MSD, Gilead, Roche, Bayer

Why should we care about Liver Cancer in NASH?

Outline:

1. Introduction - **MASLD**: the Artist formerly known as…NAFLD
2. The burden of obesity-associated Liver Cancer (HCC)
3. HCC Surveillance in patients with obesity
4. Risk cofactors of HCC development in chronic liver disease
5. Can we really reduce HCC risk in this setting?
6. Conclusions


M*A*S*H
BOSTON
SEOUL
CONEY ISLAND
SAN FRANCISCO
TOKYO

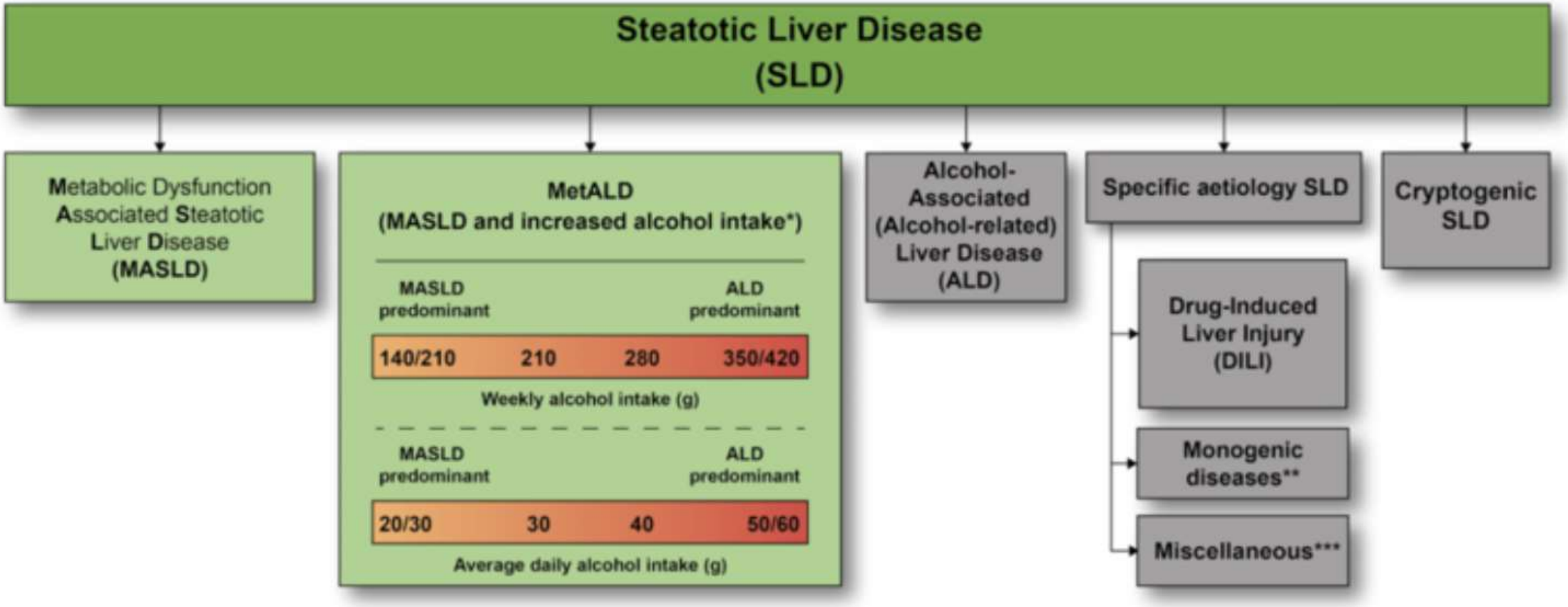

"'M·A·S·H' IS WHAT THE NEW FREEDOM OF THE SCREEN IS ALL ABOUT!"
—Richard Schickel, Life
"The funniest . . . you will be bowled over by its wit!"
—Judith Crist, NBC-TV
"'M*A*S*H' is the best American war comedy since sound came in."
—Pauline Kael, New Yorker
"'M*A*S*H' is a cockeyed masterpiece—see it twice."
—Joseph Morgenstern, Newsweek
M·A·S·H An Ingo Preminger Production
DONALD SUTHERLAND · ELLIOTT GOULD · TOM SKERRITT
Produced by INGO PREMINGER
Directed by ROBERT ALTMAN
Screenplay by RING LARDNER, Jr.
R

“...we will no longer use the previously exclusionary, negative and confounder terms that used potentially stigmatizing language of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). “

What to know about the new nomenclature:

- Steatotic liver disease (SLD) was chosen as an overarching term to encompass the various aetiologies of steatosis.
- The term steatohepatitis is an important pathophysiological concept to be retained.
- Nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (**MASLD**). MASLD encompasses patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors.
- A new category, outside pure MASLD, termed **MetALD** was selected to describe those with MASLD who consume greater amounts of alcohol per week (140 g/week and 210 g/week for females and males respectively).
- Metabolic dysfunction-associated steatohepatitis (**MASH**) is the replacement term for NASH. Those with no metabolic parameters and no known cause have cryptogenic SLD.

Steatotic Liver Disease Sub-classification



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

Rinella ME. Hepatology 2023

Liver Cancer and MASH

Introduction- MASLD: the Artist formerly known as…NAFLD

- The most common cause of liver disease worldwide in both adults and children: global prevalence **30%**
- In **20%** of MASLD patients: **MASH**, with variable degrees of fibrosis
- One of the main causes of liver cirrhosis and the most rapidly growing indication for liver transplantation in Europe and USA.
- Over the last ten years, MASLD has been the most rapidly growing contributor to liver mortality and morbidity.

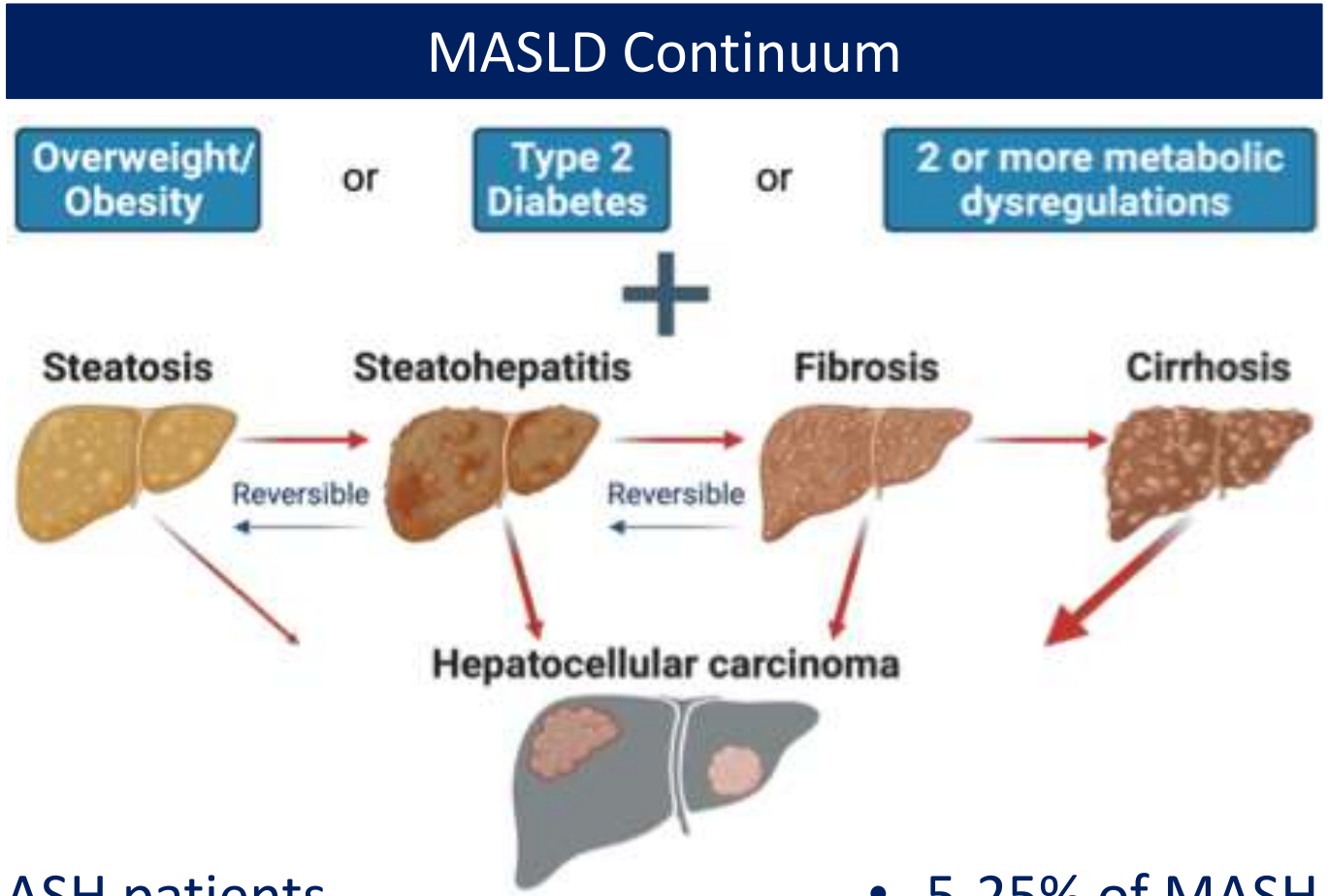
Sayiner. Clin Liver Dis 2016
Paik. Hepatology 2020

Liver Cancer and MASH

Introduction: MASLD: the Artist formerly known as…NAFLD

- **MASLD** is associated with features of Metabolic Syndrome- probability of developing **MASH** increases with number of risk factors involved (obesity, T2DM, hypertension, dyslipidemia)
- Increasing severity of **obesity** has been linked to increased risk of HCC.
- **Type 2 diabetes mellitus** is associated with an increased HCC risk, with the strongest association observed in patients with greater disease duration.
- Recent data also suggest a possible association between **hyperlipidemia** and HCC incidence.

Liver Cancer and MASH

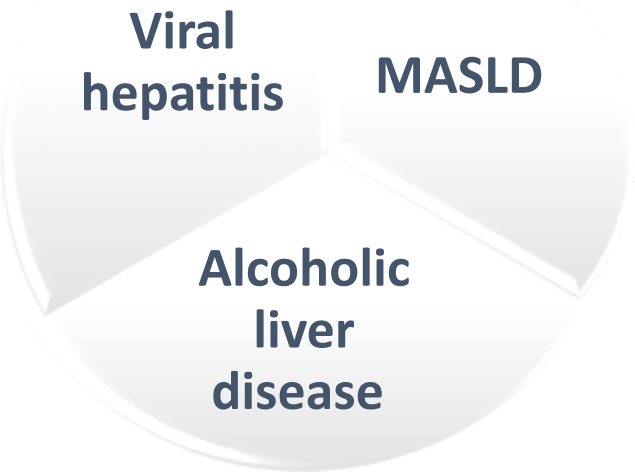


- 5-15% of obese MASH patients progress to cirrhosis
- 5-25% of MASH with cirrhosis progress to HCC

Liver Cancer and MASH

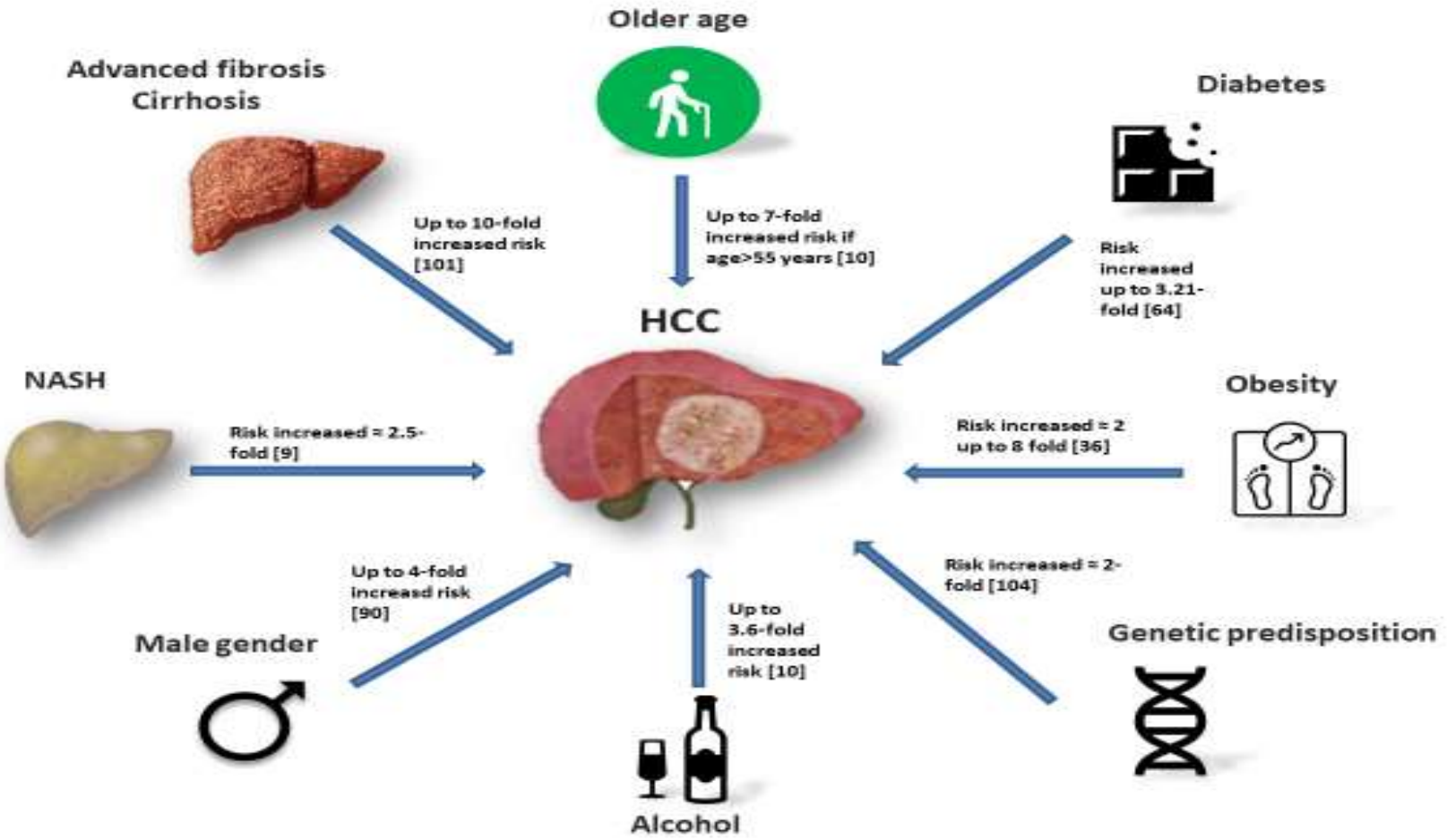
Hepatocellular carcinoma

- 5th most frequently diagnosed cancer
- 3rd highest fatality rate of all cancers
- 90% of HCC cases arise in the context of liver cirrhosis
- Annual incidence rate of HCC in MASH: 5,29 per 1000 p/y, whereas in MASLD: 0.44 per 1000 p/y
- There is a clear evidence of a constant rise in HCC incidence, which is commonly attributed to the parallel increase of MASH.



Stepanova. Clin Gastroenterol Hepatol 2017

Liver Cancer and MASH



World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2022 January 21; 28(3): 310-331

DOI: 10.3748/wjg.v28.i3.310

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

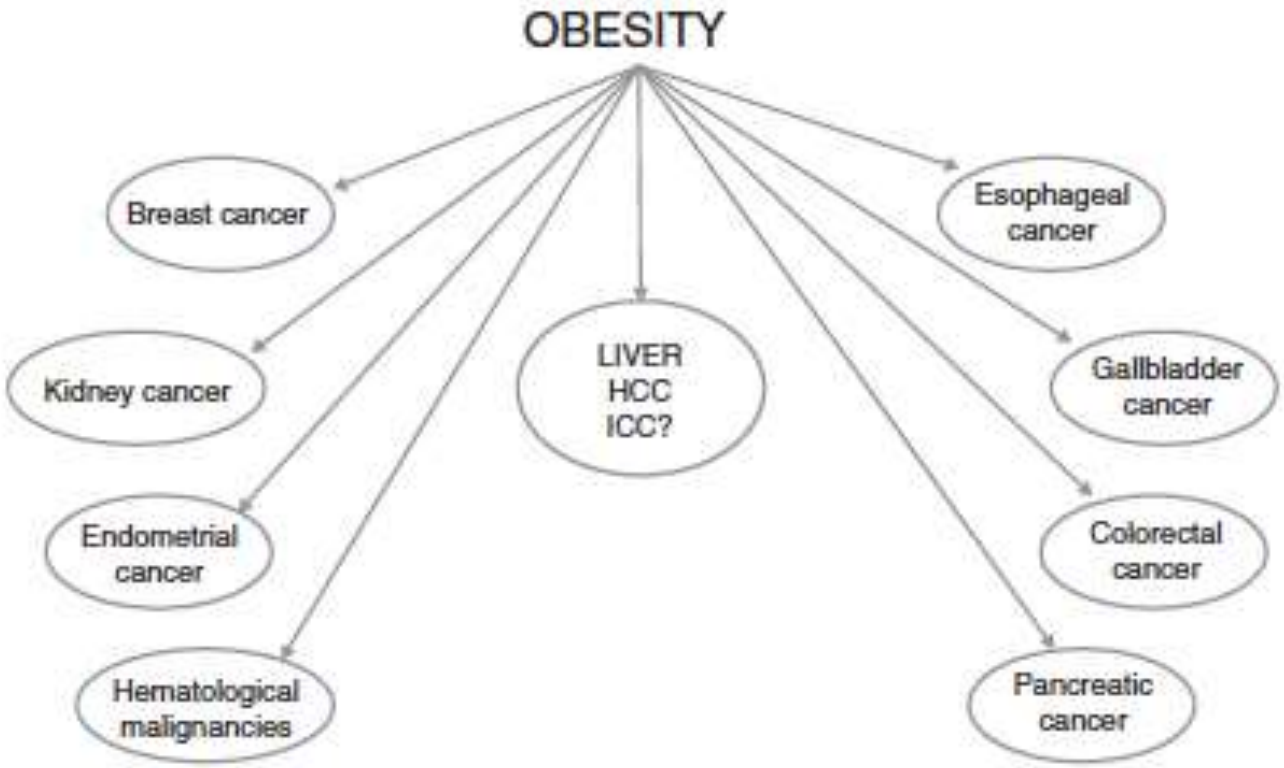
REVIEW

Non-alcoholic fatty liver disease and hepatocellular carcinoma: Clinical challenges of an intriguing link

Lampros Chrysavgis, Ilias Giannakodimos, Panagiota Diamantopoulou, Evangelos Cholongitas

Liver Cancer and MASH

The burden of obesity-associated Liver Cancer (HCC)



C. Saitta et al. / Annals of Hepatology 18 (2019) 810–815

Liver Cancer and MASH

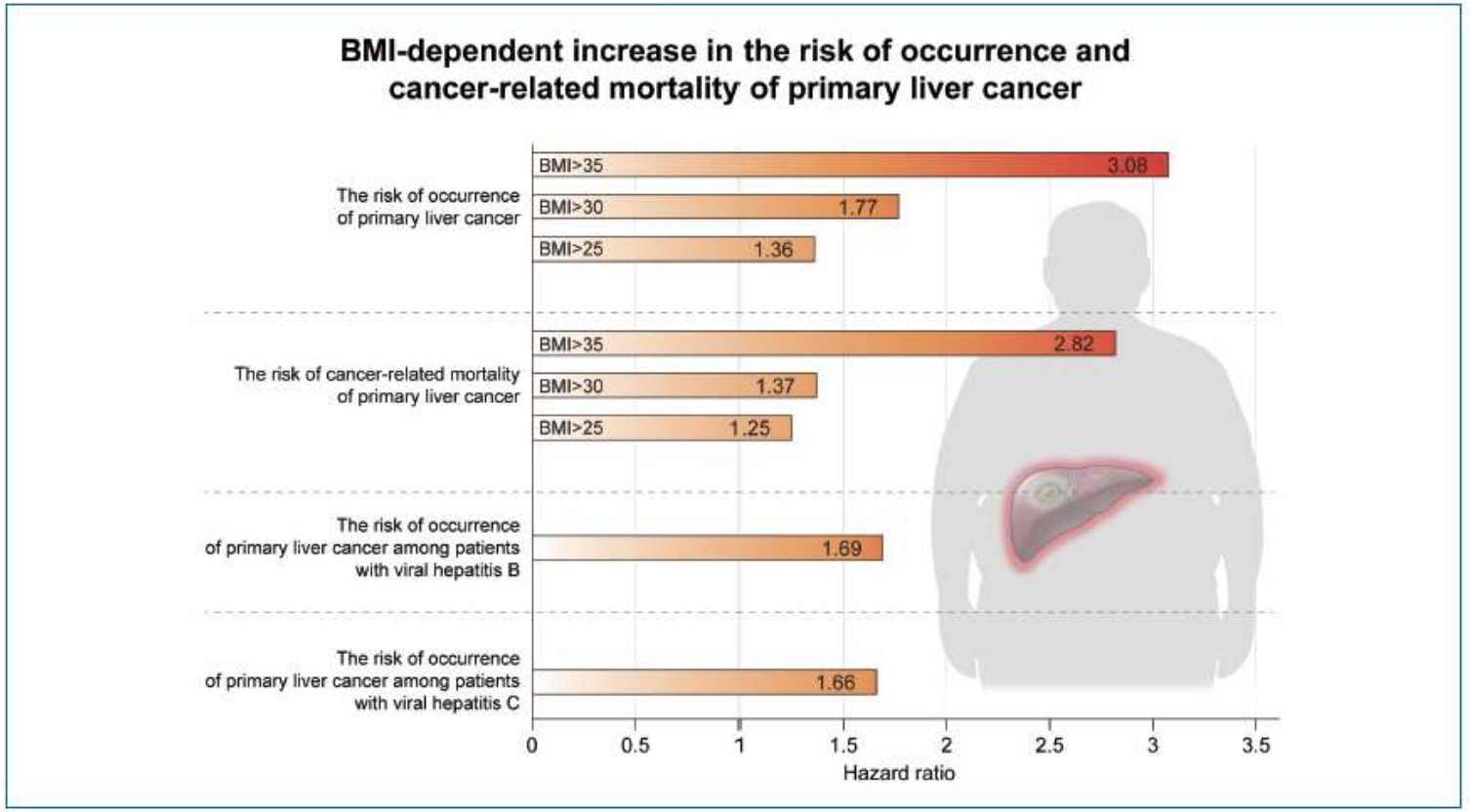
Huang. Nat Rev Gastroenterol Hepatol 2021

Liver Cancer and MASH

Obesity and the risk of primary liver cancer: A system-atic review and meta-analysis

Won Sohn[1,*], Hyun Woong Lee[2,*], Sangheun Lee[3], Jin Hong Lim[4], Min Woo Lee[5], Chan Hyuk Park[6], and Seung Kew Yoon[7]

CLINICAL and MOLECULAR HEPATOLOGY



Liver Cancer and MASH

The burden of obesity-associated Liver Cancer (HCC)

- Metanalysis of 9 observational studies (>1,5M individuals) showed that patients with obesity had 2 fold increase in HCC related mortality

- In HCC treated with OLT, increased incidence of life-threatening complications in overweight / obese patients: 15% X 7%

- Retrospective US cohort of 342 HCC showed that BMI>30 was a predictor of recurrence, microvascular invasion and poor overall survival (doubling mortality)

Gupta, Am J Clin Oncol 2018
Siegel, Tranplant 2012

Pathophysiological mechanisms of obesity – associated HCC

- Insulin resistance and hyperinsulinemia (↑serum level / biological activity of IGF-1)
- Lipid accumulation and lipotoxicity (driver of inflammation)
- Adipose tissue and adipokines (accumulation of macrophages, pro inf CK, pro fibrotic CK)
- Endoplasmic reticulum stress (positive feedback enhanced lipogenesis)
- Oxidative stress (excessive levels of Reactive Oxygen Species)

Pathophysiological mechanisms of obesity – associated HCC

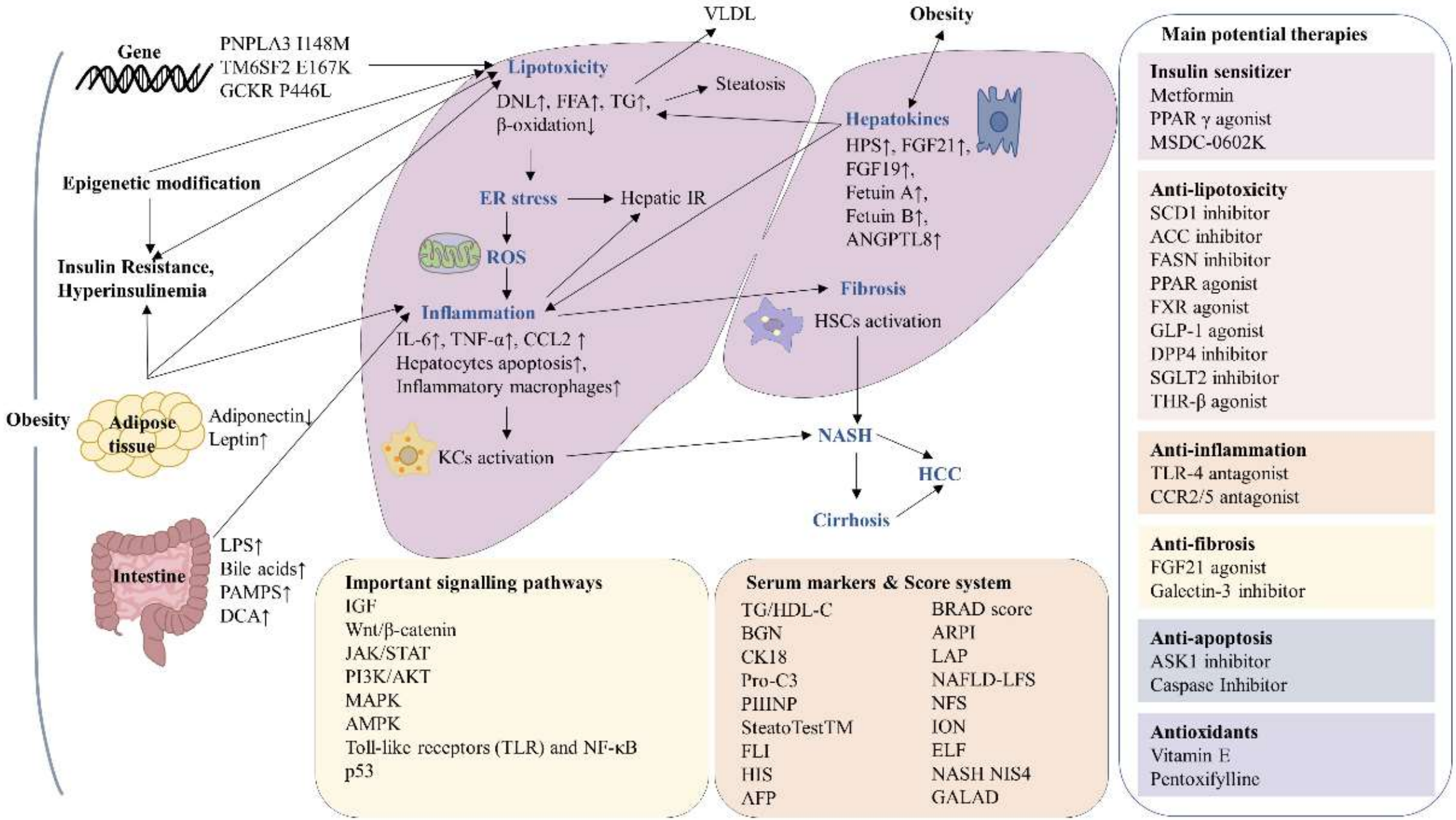
- Imbalance of intestinal microbiota (lipopolysaccharide in portal blood)
- Inflammation and immune response (CK from liver and fat tissue)
- Autophagy (lysosome dependent catabolic process, profibrogenic properties in HSC)
- Hepatokines (hepassocin, ANGPTL 8, Fetuin A and B, FGF 19/21)
- Genetic factors
- Epigenetic modification (regulation of gene expression via DNA methylation, histone modification and microRNA)

Obesity, non-alcoholic fatty liver disease and hepatocellular carcinoma: current status and therapeutic targets

Yinshuang Chen[1,2], Weipeng Wang[2], Maria P. Morgan[1], Tracy Robson[1*] and Stephanie Annett[1*]

IFSO NAPOLI 2023

Chen Y Front. Endocrinol.. 2023



Chen Y Front. Endocrinol.. 2023

Liver Cancer and MASH

HCC Surveillance in patients with obesity

- Surveillance aims reduction in mortality through an early diagnosis, with a cost-effective strategy
- Screening for HCC is currently recommended for all patients with cirrhosis or advanced fibrosis (abdominal US q 6M, alpha-fetoprotein). EASL Guidelines, J Hepatol 2018
- Nevertheless, surveillance in patients with MASLD is often suboptimal, with up to 52% of HCC cases not diagnosed by screening and presenting with liver-related complications instead.

Abdominal ultrasound is not as sensitive as an early detection tool since the presence of fatty liver disease and obesity hampers its performance.

Piscaglia. Hepatology 2016
Del Poggio. Clin Gastroenterol Hepatol 2014

Liver Cancer and MASH

HCC Surveillance in patients with obesity

- There is the potential for HCC to arise in non-cirrhotic livers.
- Even so, the incidence of HCC in noncirrhotic individuals is considered insufficient to justify routine screening in such patients, considering the very high prevalence of **MASLD** in the general population.

Timely diagnosis of HCC arising in individuals with MASLD is a true challenge for hepatologists and obesity makes it even more difficult

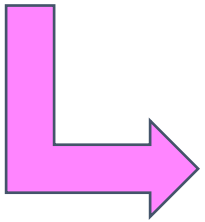
Simmons. Aliment Pharmacol Ther 2017

Liver Cancer and MASH

HCC Surveillance in patients with obesity

- Even facing a dismal prognosis, patients with **MASLD**-related HCC should be treated based upon BCLC staging.

- Patients with **MASLD**-HCC generally have a worse prognosis than those whose HCC has been attributed to some other etiology.



- More advanced stage of disease at diagnosis
- Patients older and with more co-morbidities

Than. Qjm 2017

Liver Cancer and MASH

HCC Surveillance in patients with obesity

- A significantly higher proportion of patients with **MASLD** related HCC (57%) did not undergo surveillance in 3 years preceding HCC diagnosis, compared with patients with alcohol (42%) or HCV related disease (13%)

- Retrospective US study, 941 pts in screening, showed that obese pts had 3-8 fold higher risk of having inadequate examination

  Increasing BMI ⟶ increased risk of failure

S Mittal, Clin Gastro Hepatol 2015

Simmons, APT 2017

Liver Cancer and MASH

Risk cofactor of HCC development in chronic liver disease

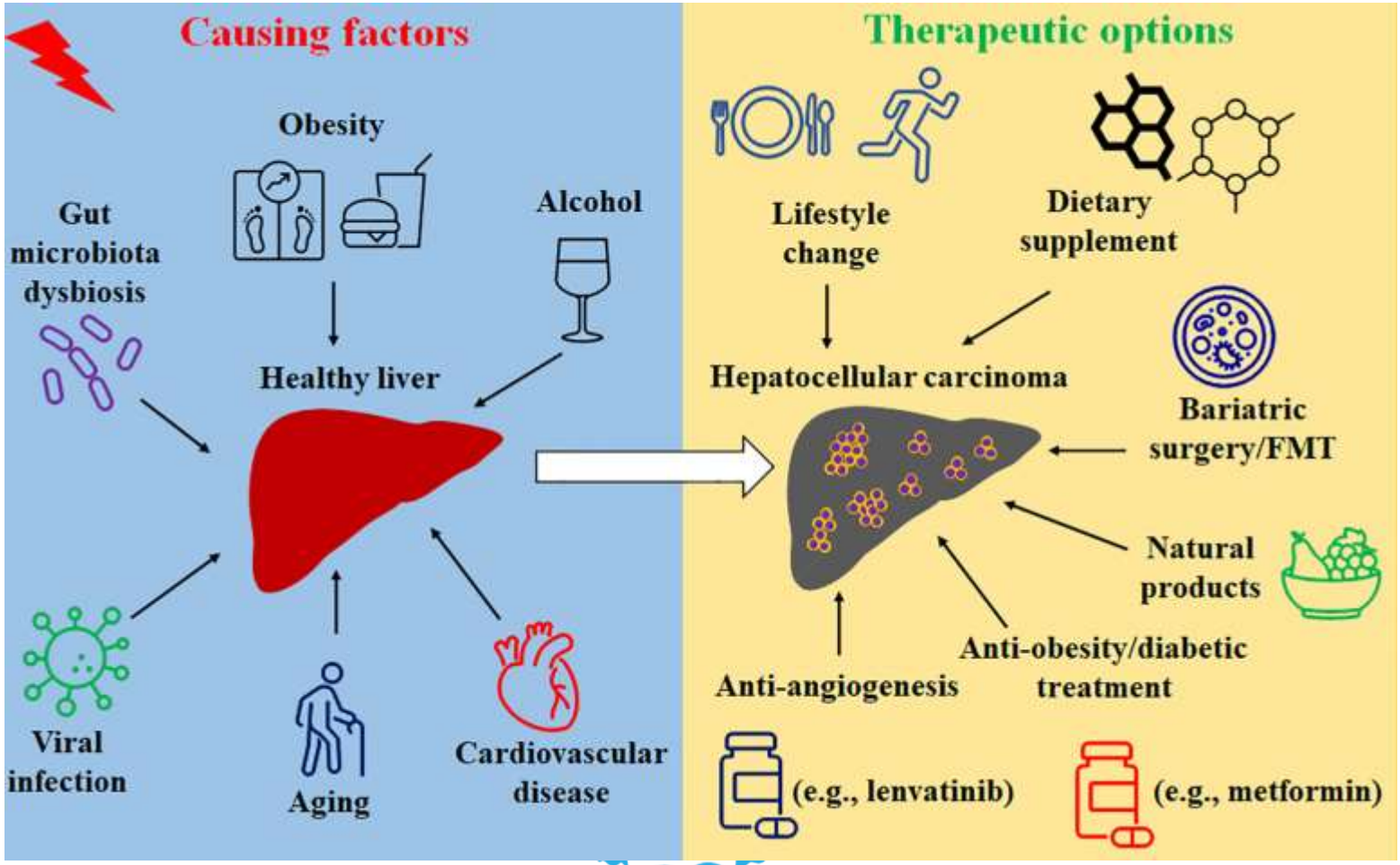
- Obesity increases 4 fold risk of HCC in HCV +, 1.4 fold in HBV+, 2 fold if no viral infection
- Obesity +2TDM increases risk 100 fold in viral hepatitis pts
- Imaging detection of **MASLD** in Hep B pts, increases risk for HCC
- French retrospective study of 110 pts : alcoholic cirrhosis, who were obese with OLT, had increased risk of HCC of 6 fold, and the presence of T2DM significantly increases HCC risk development

Cho, J Clin Gastro 2019

Pais, Clin Gastro Hepatol 2015

Liver Cancer and MASH

Can we really reduce HCC risk in this setting



Liver Cancer and MASH

Conclusions

- With the growing epidemic of obesity, a parallel increase in **MASLD** is foreseen
- It impacts the risk of HCC by exacerbating the onset and progression of **MASLD**, and is associated with reduced survival in HCC pts
- This also might be related to a less efficient surveillance strategy and consequent delay in diagnosis with more limited probability of therapeutic interventions

Liver Cancer and MASH

Conclusions

- Combining lifestyle, pharmaceutical and/or endoscopic/surgical therapies, most likely will yield superior long term HCC prevention through durable and sustained weight reduction

- Improving mechanistic understanding of the impact of these therapies in liver health, may allow new insights in therapeutic targets for **MASH** treatment and HCC prevention