Updates from the AASLD

Washington

Rob Goldin
Imperial College

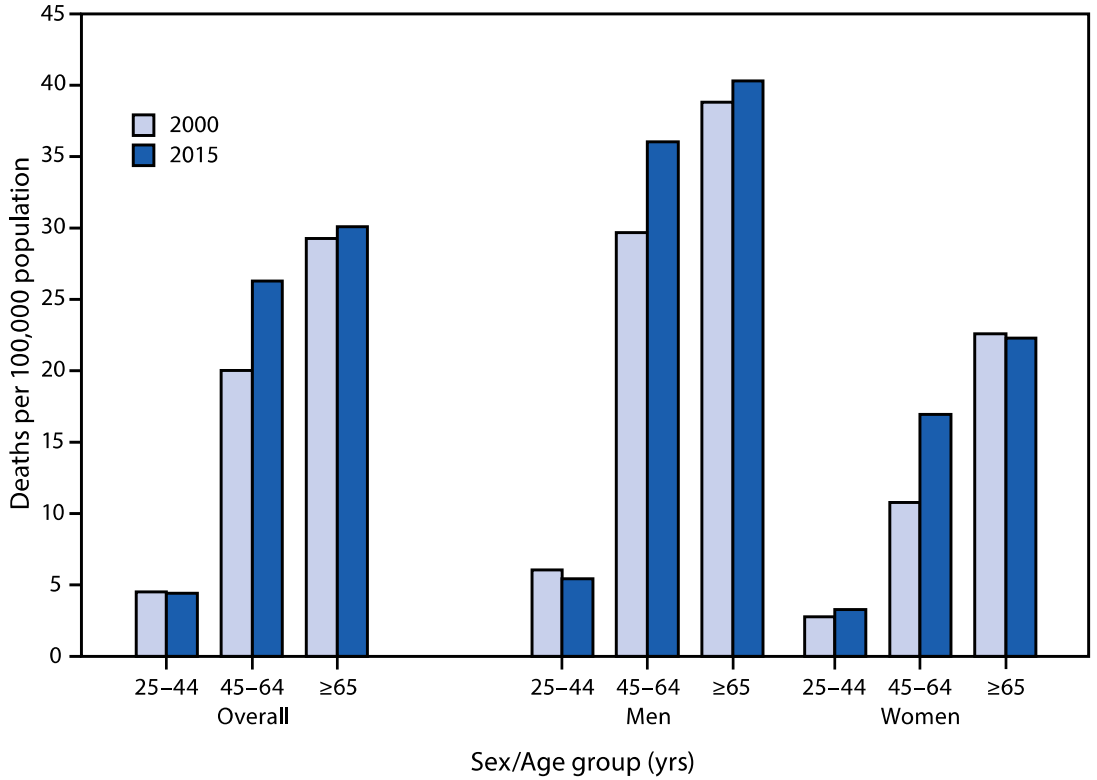
Centers for Disease Control and Prevention

- Death rates for chronic liver disease and cirrhosis rose 31% among those age 45 to 64 between 2000 and 2015.
- Cases of liver cancer rose more than 20% in the U.S. between 1990 and 2015. “With baby boomers, we may focus on heart disease, dementia and cancer, and don’t always think about the liver,”

Anna S. Lok,

Director of Hepatology at the University of Michigan and President of the American Association for the Study of Liver Diseases

Death Rates* for Chronic Liver Disease and Cirrhosis,† by Sex and Age Group — National Vital Statistics System, United States, 2000 and 2015



* Rates per 100,000 population.

† Chronic liver disease and cirrhosis deaths were identified with *International Classification of Diseases, Tenth Revision* (ICD-10) codes K70 and K73–K74.

Inflammatory Diseases

Histological features predicting progression in AI Hepatitis

- 66 patients with sequential biopsies.
- At the time of diagnosis, 7% were cirrhotic.
- Fibrosis progressed in 42% patients, remained stable in 39% and resolved in 18% patients.
- **Risk factors for fibrosis progression:**

  baseline total inflammation (OR 1.7)

  cumulative total inflammation (OR 1.8)

  rosette formation (OR 2.8)

  absence of pericholangitis (OR 0.4) and

  necrosis (OR 1.4)

Histological features predicting progression in AI Hepatitis

Risk factors for cirrhosis were:

cholestasis (OR 4.6),

interphase inflammation (OR 3.4) and

necrosis (OR 3.3)

None of the patients with histological pericholangitis or granulomas developed cirrhosis.

Immune reconstitution inflammatory syndrome (IRIS)

A disease-specific or pathogen-specific inflammatory response in HIV-infected patients after initiation/reinitiation of ART or a change to more active ART.

It is accompanied by a rapid rise in CD4 count and/or a rapid decrease in HIV viremia.

Most clinically apparent cases occur in patients with low CD4 counts and high viral loads.

Presentation is usually within the first 4 to 8 weeks after ART initiation and inflammatory reactions to many pathogens are described

In low-income and medium-income countries TB-IRIS is frequent.

Two forms:

paradoxic, in which IRIS occurs in those who start TB treatment before ART

unmasking, which occurs in those with undiagnosed TB who start ART.

A meta-analysis estimated the pooled cumulative incidence as 15.7%. of patients starting ART while on TB treatment develop paradoxic TB-IRIS

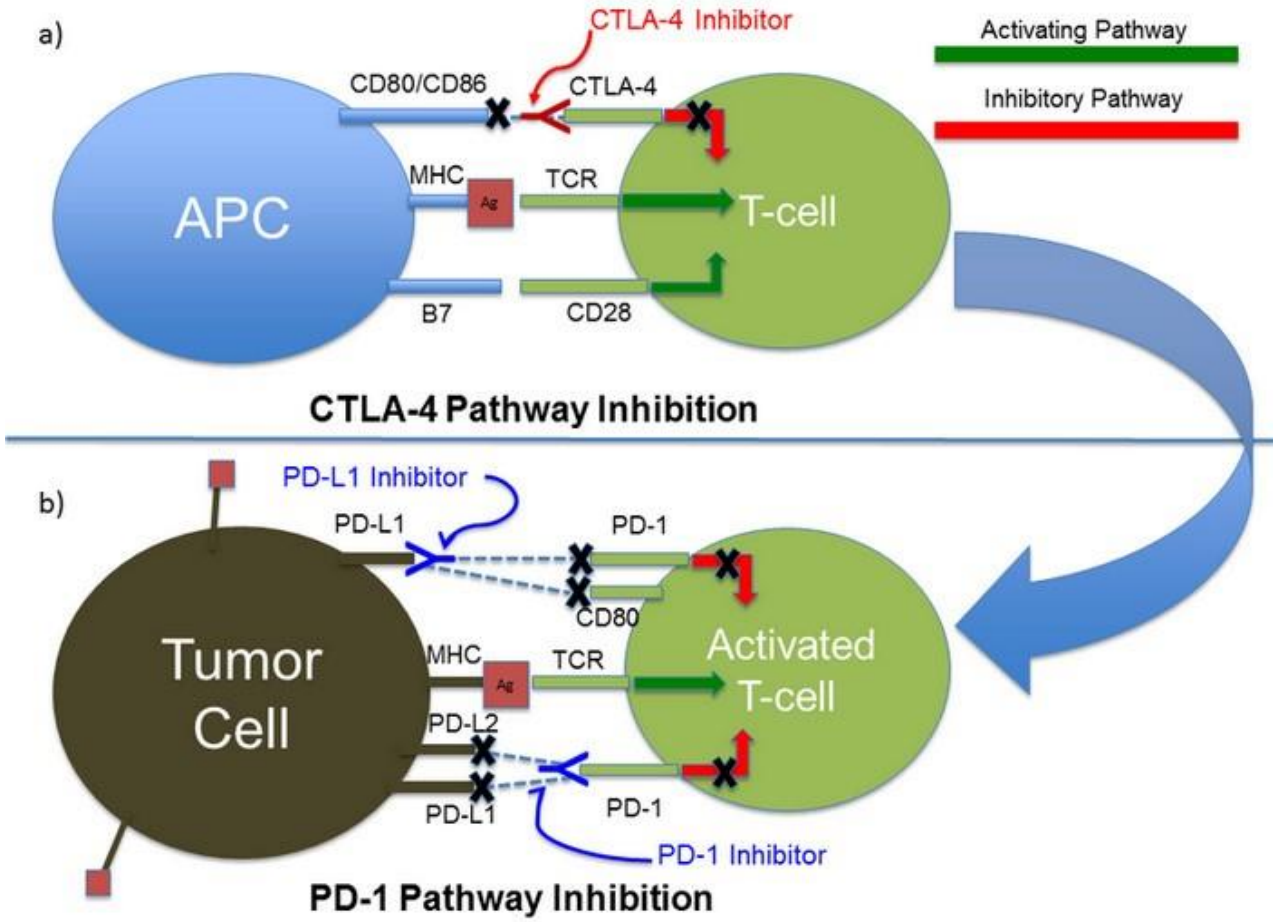
The case fatality rate was 11%

In a case series of patients with hepatic TB-IRIS, presentations were characterized by hepatomegaly (56%) and an abnormal liver profile, with two-thirds having a fever.

The pattern of liver enzyme abnormality was a mixed picture with moderate elevation of ALT/AST but a more significant elevation in GGT over ALP.

Histologic features observed include increased numbers of granulomas per liver core with abundant eosinophils palisading around these granulomas

Acute liver injury due to immunotherapy for metastatic cancer: a new challenge



Acute liver injury due to immunotherapy for metastatic cancer: a new challenge

1425 patients treated with immunotherapy

1.3% were referred to the liver unit for grade 3-4 hepatitis.

3 were excluded (acute HEV hepatitis, tumour liver infiltration, absence of liver biopsy).

Clinical and biological data were collected. Two blinded pathologists performed histological review.

- 56% pts received anti-PD1/PD-L1 and 44% pts anti-CTLA4 therapy
- Time between therapy initiation and hepatitis onset was 5 [1-49] weeks, median number of injections was 2 [1-36].
- No patient developed hepatic failure.
- Antinuclear and anti-smooth muscle auto-antibodies ≥1:80 were found in 50% and 19%, respectively.
- RUCAM scale for causal relationship: in 14 (87.5%) the association was highly probable and in 2 (12.5%) was probable.

Acute liver injury due to immunotherapy for metastatic cancer: a new challenge

- **Histology related to anti-CTLA4:**

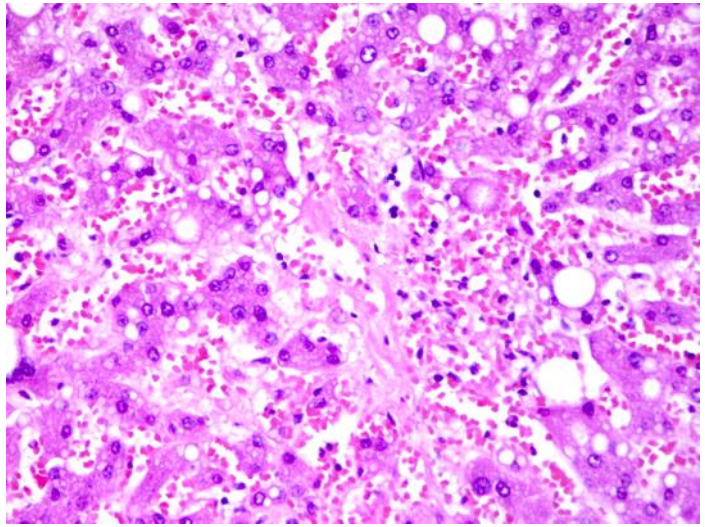
  poorly delimitated granulomas, including fibrin ring granulomas,
  severe lobular necrotico-inflammatory activity and
  central vein endothelitis

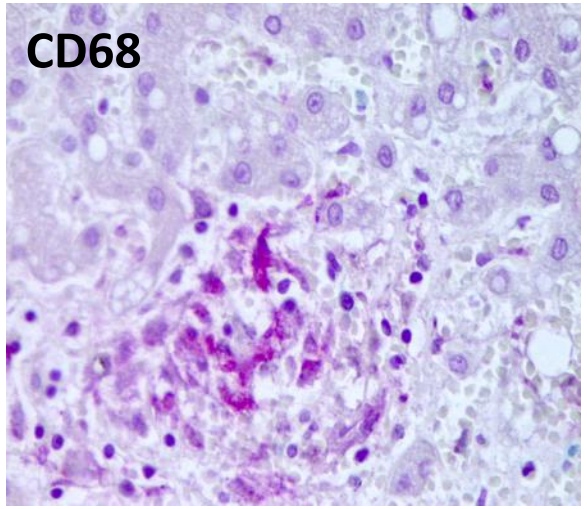
- **Histology related to anti-PD1/ PD-L1:**

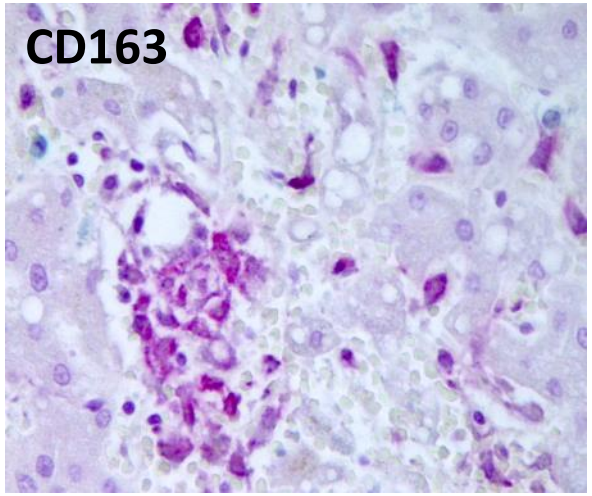
more heterogeneous with lobular hepatitis and mild to moderate portal activity.

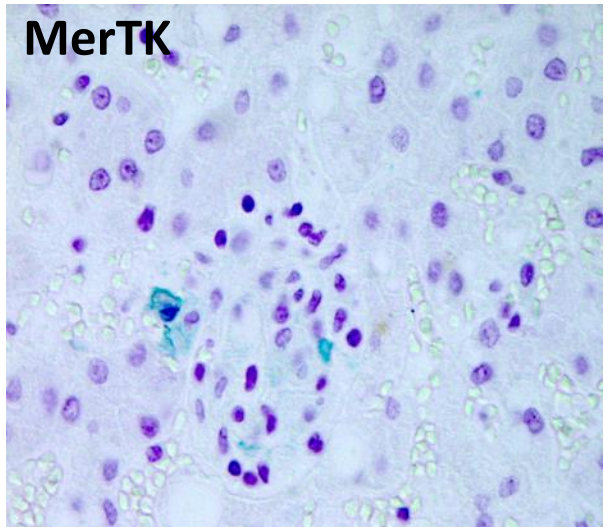
In both cases, bile duct injuries with lymphocytic cholangitis were found.
Immunostainin g found a prevalent CD8+ lymphocyte infiltrate.

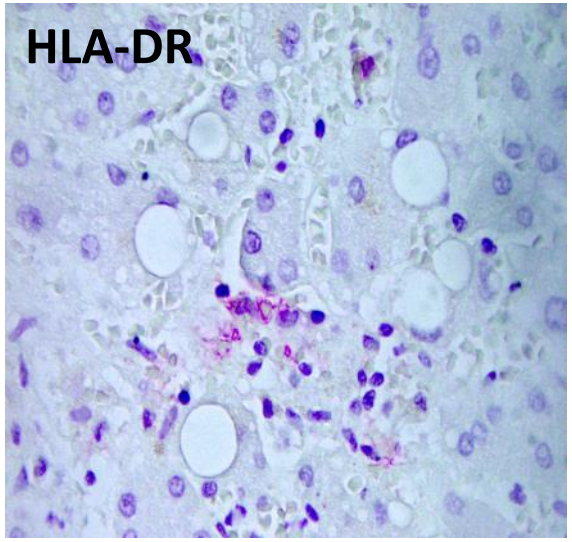
H&E











- The management was tailored according to the severity of liver injury:

  50% improved either spontaneously or with maintenance of low dose steroids

  50% received steroids therapy +/- addition of a second immunosuppressive drug

  In 3 the immunotherapy was safely reintroduced.

Conclusion

- Acute hepatitis due to immunotherapy for metastatic cancer is:
- rare (1.3%) and mostly not severe.
- histological assessment can distinguish between anti-PD1/PD-L1 and anti-CTLA toxicity.
- management should be tailored according to patient's severity and that 50% of patients did not require high dose of steroids.

Patterns in Ayurveda and Herbal Induced Liver Injury

- Ayurvedic and herbal products (AHP) are known to cause varying degrees of liver injury
- histopathological patterns of liver injury due to AHP is not well studied.
- 94 patients (6.52%)diagnosed with AHP liver-injury, by RUCAM
- 27 patients (28.7%) underwent biopsy

- Autoantibodies positive in 37%

Patterns in Ayurveda and Herbal Induced Liver Injury

- Hepatocellular, cholestatic and mixed patterns seen in 59.3%, 7.4%, 33.3%, respectively
- 22.2% died
- Presence of necrosis and steatosis on biopsy associated with higher mortality
- 100% mortality with panacinar submassive and massive necrosis

Large Print Guide

Ayurvedic Man Encounters with Indian medicine

Exhibition texts

16 November 2017–08 April 2018

Once finished please leave in the box provided outside the exit

A copy of this guide is available for download from **wellcomecollection.org/ayurvedicman**

Disease outcomes in a cohort of women in Ireland infected by hepatitis C-contaminated anti-D immunoglobulin during 1970s

- Women with chronic HCV from contaminated anti-D in the 1970s in Ireland.
- 19% developed cirrhosis and 5% died from liver-related causes after 36 years.
- Disease progression accelerated over time, particularly with high alcohol use

Clinical Characteristics and Outcome of Hepatic Sarcoidosis

- A cohort of incident cases of sarcoidosis in Olmsted County, MN, USA, from 1976 to 2013 was identified from the database. Diagnosis was verified by individual medical record review. Confirmed cases of sarcoidosis were then reviewed for liver involvement. A total of 345 cases of incident sarcoidosis were identified.
- 6% had liver involvement (mean age 46 years, 53% female and 79% Caucasian).
- Most patients had asymptomatic liver disease and were discovered in pursuit of abnormal biochemical tests and imaging studies.
- Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were elevated in the majority of patients .
- About half of patients had abnormal imaging study with hypodense nodular lesions being the most common abnormality followed by hepatomegaly
- Liver biopsy revealed non-caseating granuloma in 88%.
- A total of four patients developed cirrhosis.

Cancer

Clinicopathological characteristics and mutational profile of PD-L1 positive hepatocellular carcinoma

PD-L1-positive HCCs was significantly more frequently associated with:

- portal vein thrombosis
- moderately/poorly differentiated phenotype
- with infiltration of CD8+ lymphocyte and
- CK-19 and SALL-4 expression

HBV-associated intrahepatic cholangiocarcinomas

- In Eastern countries, a newly identified major risk factor of iCCA is viral hepatitis infection
- HBV - associated iCCA is a malignancy with distinctive characteristics between hepatocellular carcinoma and iCCA:

  younger age,

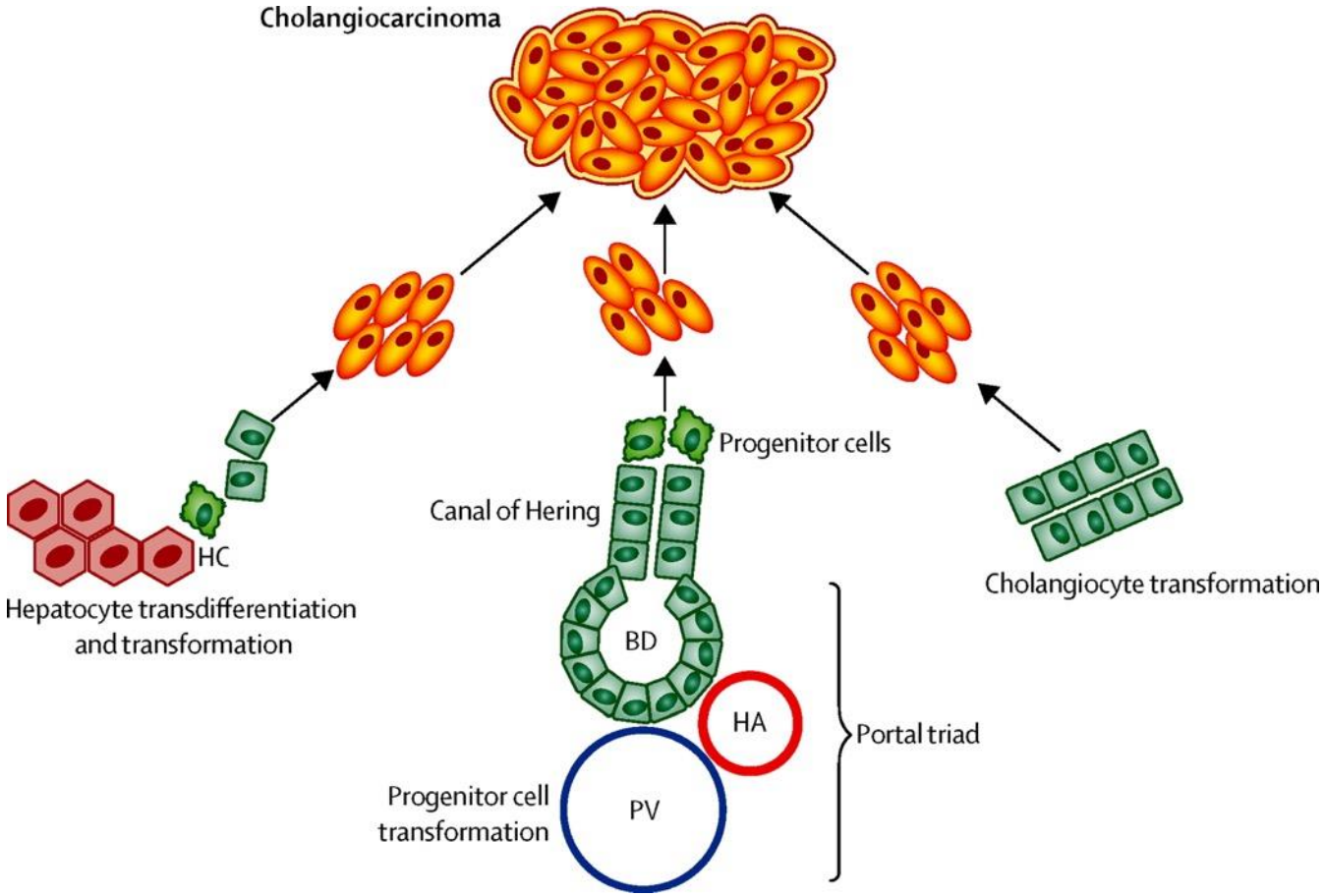
  a predominance of male patients,

  frequent elevation of alpha-fetoprotein

  infrequent lymph node metastasis

HBV-associated intrahepatic cholangiocarcinomas

- In addition, survival outcomes of patients with HBV-associated iCCA have been found to be significantly better than those without HBV infection after hepatic resection
- Most importantly, the representative hallmark of iCCA, lymph node metastasis, which significantly worsens prognosis and critically contributes to the tumor recurrence after surgical resection, has been found to be significantly more infrequent in HBV-associated iCCA



Combined Hepatocellular-Cholangiocarcinoma

- Combined hepatocellular-cholangiocarcinoma (CHC) is a rare tumor with poor prognosis, with incidence ranging from 1.0%-4.7% of all primary hepatic tumors.
- This entity will be renamed as hepato-cholangiocarcinoma.
- The known risk factors for hepatocellular carcinoma have been implicated for CHC.

- World J Hepatol. 2017 Feb 28; 9(6): 300–309.

Combined Hepatocellular-Cholangiocarcinoma

- Heterogeneous and overlapping imaging features of HCC and cholangiocarcinoma should raise the suspicion for CHC and multiple core biopsies are recommended before administering treatment.
- There is sufficient data to support bipotent hepatic progenitor cells as the cell of origin for CHC.
- The current World Health Organization classification categorizes two main types of CHC based on: Classical type and CHC with stem cell features.

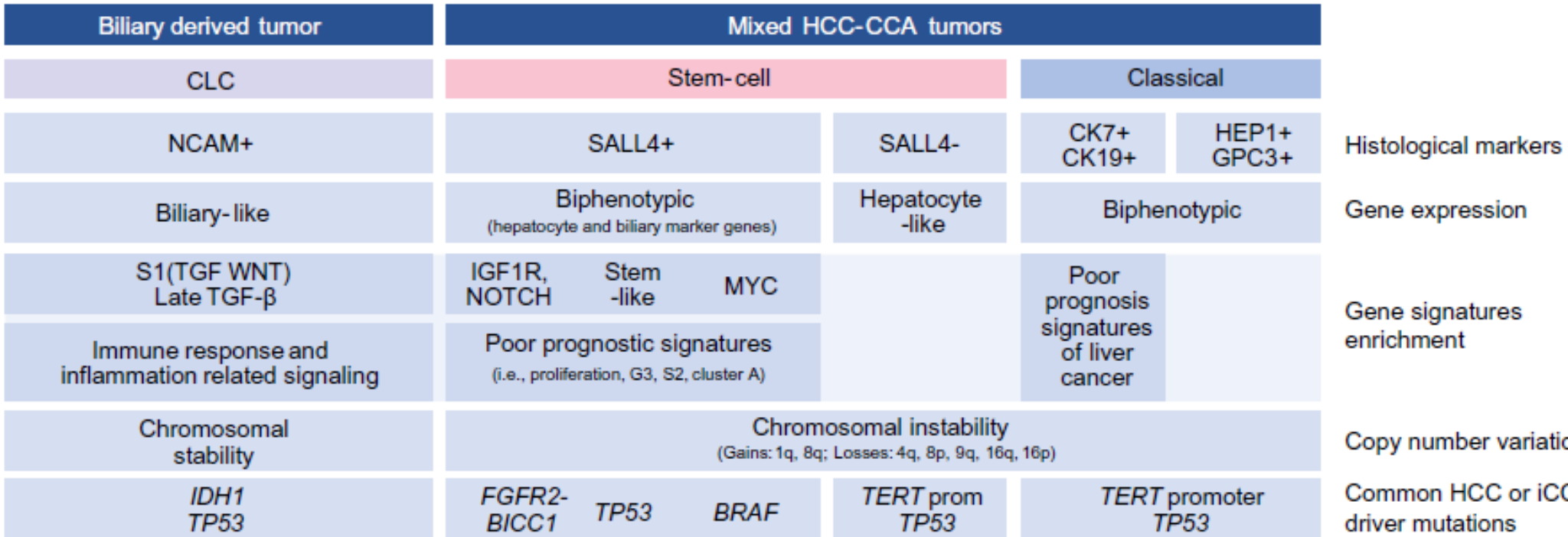
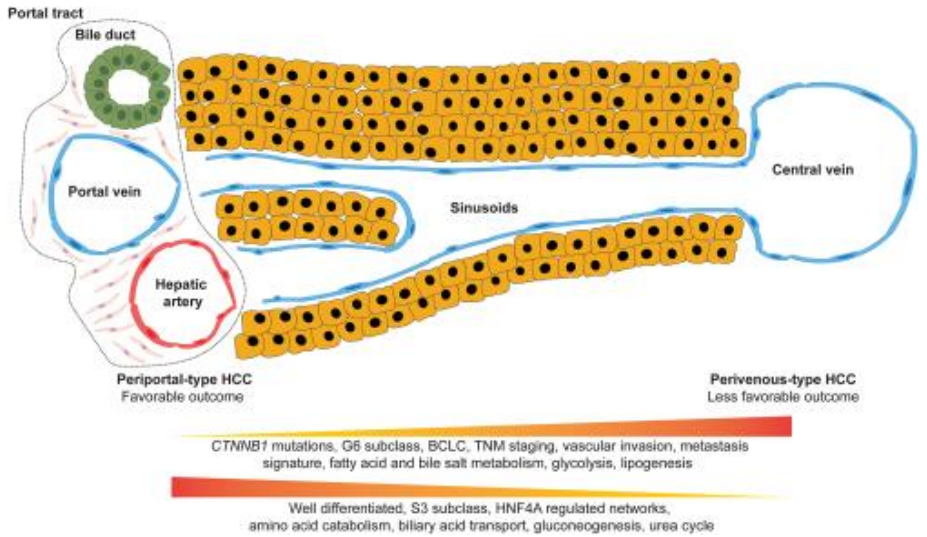


Fig. 7. Summary of molecular characterization of mixed HCC-CCAs and CLC tumors as distinct entities. CLC only share biliary-derived features, as opposed to HCC-iCCA tumors. Specific cell lineage markers, liver cancer derived gene signatures, pathway signaling, chromosomal stability and driver mutations are depicted for each entity.

Molecular classification of hepatocellular carcinoma: The view from metabolic zonation



Hepatology
Volume onlinelibrary.wiley.com/doi/10.1002/hep.29311/full#hep29311-fig-000166, Issue 5, pages 1377-1380, 29 SEP 2017 DOI: 10.1002/hep.29311
http://

- Well-differentiated, potentially low-aggressiveness tumors form the heterogeneous molecular class of nonproliferative HCCs, characterized by an approximate 50% β-catenin mutation rate.
- Nonproliferative HCCs preserve the zonation program that distributes metabolic functions along the portocentral axis in normal liver.
- two well-differentiated, nonproliferation subclasses:

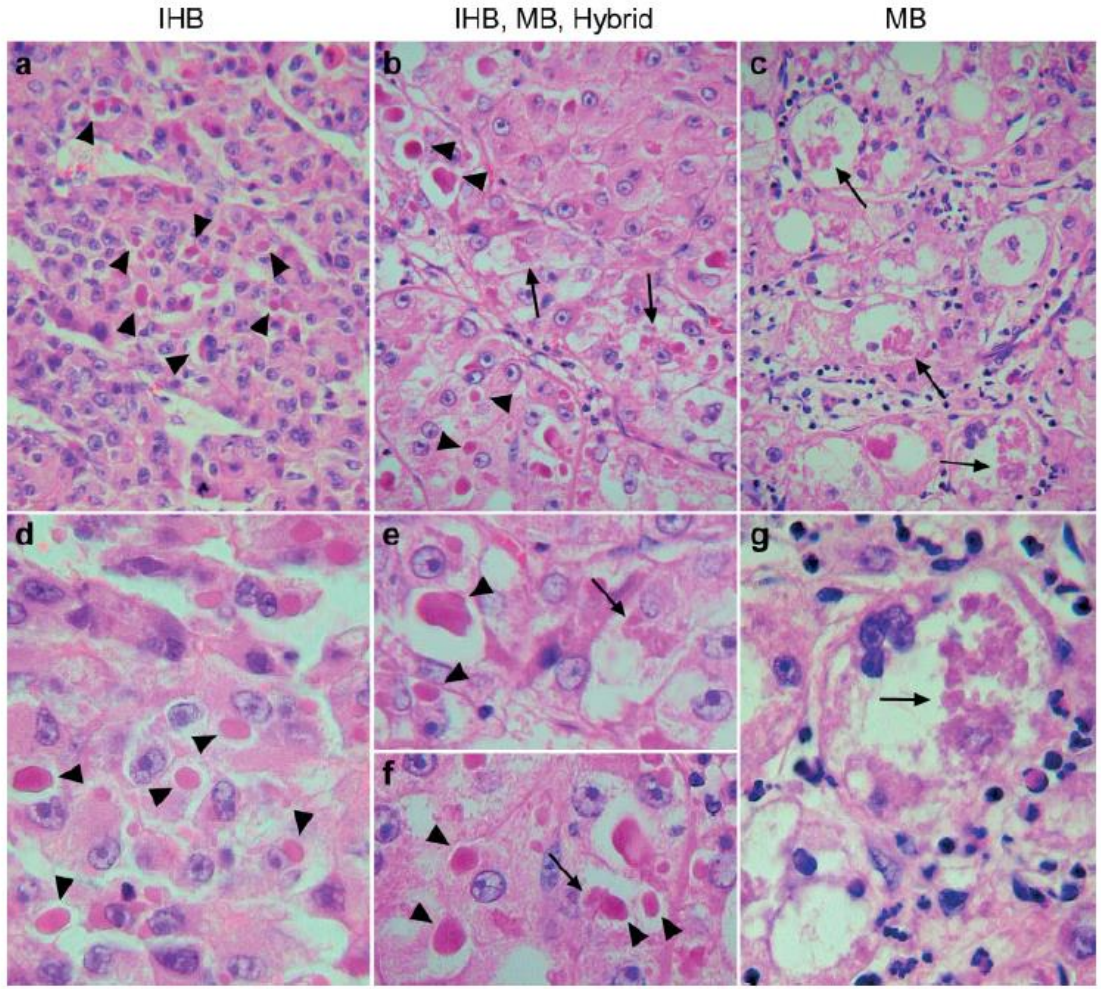
  periportal-type (wild-type β-catenin) and

  perivenous-type (mutant β-catenin)

The new periportal-type subclass

- represented 29% of all HCCs
- expressed a hepatocyte nuclear factor 4A-driven gene network
- early-stage
- no macrovascular invasion; and
- showed the lowest metastasis-specific gene expression levels and TP53 mutation rates.

Inclusion bodies in HCC



J Pathol 2006; **208**: 653–661

Inclusion bodies in HCC

- Mallory-Denk and intracellular hyaline bodies (MDBs and IHBs respectively) are cytoplasmic inclusions found in hepatocellular carcinomas (HCC) of unknown prognostic relevance.
- MDB and IHB contain p62 and other proteins. Because p62 is an autophagy substrate, overexpression of p62—which might be involved in formation of p62-containing protein aggregates—is considered a marker of impaired autophagy implicated in the development of human HCC.
- Our study results indicate that HCCs which contain IHB have worse prognosis than HCCs without IHB.
- Multivariate analysis identified IHB and macroscopic vascular invasion as independent prognostic factors in patients with HCC undergoing partial liver resection.

False positive radiological diagnoses of HCC

High-risk patients with tumors > 1 cm with one or two image findings consistent with HCC and tumors < 1 cm with two or more image findings consistent with HCC with persistently increased serum alpha-fetoprotein levels above the normal range underwent liver resection.

The false-positive rate was 2.2%

0.8% were diagnosed with benign conditions: haemangioma, inflammation, cortical adenoma, dysplastic nodule, angiomyolipoma, bile duct adenoma, and non-neoplastic liver parenchyma

1.3% were diagnosed with malignancies: cholangiocarcinoma, hepatoblastoma and lymphoepithelioma-like carcinoma, ovarian cystadenocarcinoma, and nasopharynx carcinoma metastasis.

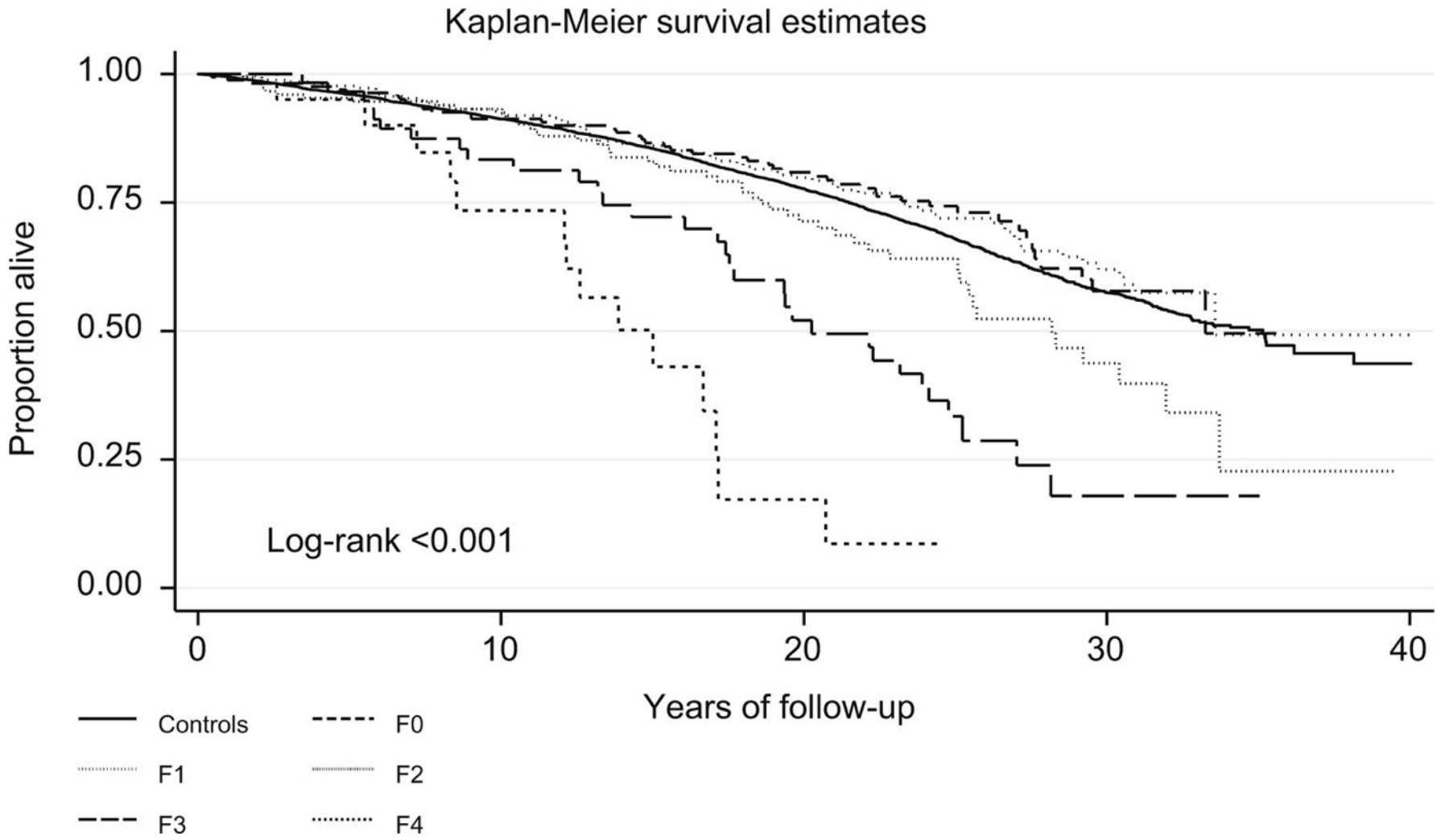
Racial Disparity in Risks for Liver Cancer

- The incidence of hepatocellular carcinoma (HCC) is increasing in the United States and has doubled over the last 2 decades.
- Chronic hepatitis B virus (HBV) correlates with HCC in most areas around the globe and in specific ethnic groups in the United States, particularly Asian Americans, due to vertical transmission of HBV at birth.
- Most patients in the United States who develop HCC have HCV with cirrhosis
- New nucleotide/nucleoside and protease inhibitors that clear HCV viral loads should, theoretically, reduce HCC over time for those who can obtain the expensive treatment
- Rates of NAFLD are highest among Hispanic patients

Fatty Liver Disease

Advanced Nonalcoholic Fatty Liver Disease. Impact of Fibrosis Severity on Major Clinical Outcomes.

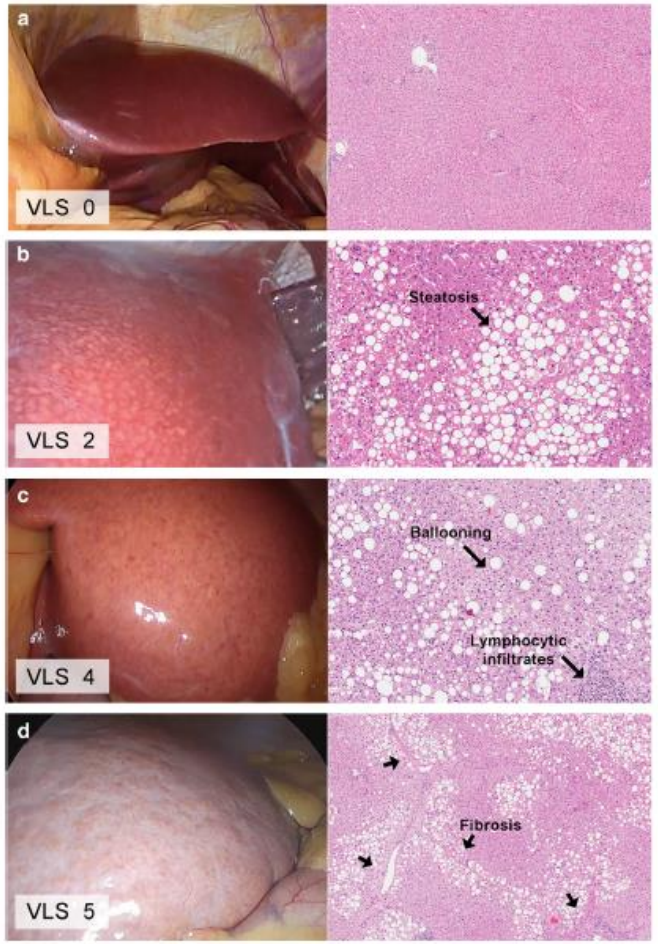
- Among cirrhotic patients, a total of 38% first major events occurred, most commonly hepatic decompensation (70%) and HCC (17%).
- Among F3 patients, a total of 26 first events occurred, of which 38% and 35% were related to non-hepatic malignancies and vascular events.
- Cirrhosis increased the risk of death/transplant, decompensation, and HCC by 4.3,4.5 and 3.9 folds respectively, but was associated with a lower risk of vascular events
- Interestingly in the cirrhotic cohort, steatosis ≥33% but not lobular inflammation or ballooning was independently associated with better overall survival and lower rates of liver-related complications



Journal of Hepatology 2017 vol. 67 j 1265–1273

Visual Liver score

Colour
Size
Surface



Obes Surg. 2017 Aug 3. doi: 10.1007/s11695-017-2859-3.

- Steatosis was most accurately identified (AUROC 0.746)
- NASH was identified with moderate accuracy (AUROC 0.746)
- Stratification into low (≤ 1) and high-risk (≥ 4) scores accurately identified patients who should or should not have an intraoperative biopsy.
- Most patients with a normal appearing liver did not have disease (94.4%)
- The structured visual assessment was quick and interobserver agreement was reasonable (κ = 0.53).

Prevalence and Clinical Characteristics of Nonalcoholic Fatty Liver Disease in Lean Subjects in Comparison with Overweight or Obese Individuals

approximately 10-20% of lean individuals also develop NAFLD

- Out of 16,398 health check-up examinees between 2008 and 2016, we enrolled 12,002 subjects without known liver disease or significant alcohol consumption.

- All subjects were categorized into three subgroups according to their body mass indexes: group 1 (BMI <23 kg/ M2), group 2 (23≤ BMI <25) and group 3 (BMI ≥25).

- Risk factors for NAFLD in group 1:
  - age
  - female
  - impaired fasting glucose
  - hypertension
  - metabolic syndrome
  - uric acid.
- In group 1, noninvasive indices less severe disease:
  - systemic inflammation,
  - insulin resistance
  - liver fibrosis
  - extrahepatic manifestations

- Only a fraction of heavy drinkers develop cirrhosis. A number of factors have been implicated in determining individual responses to alcohol, including genetics, amount and type of alcohol consumed, pattern of drinking, and metabolic syndrome.
- The main finding of the study was that, after adjustment for average daily alcohol intake and age, the risk of liver-related events was higher among weekly binge drinkers and monthly binge drinkers compared with people who engaged in less-frequent binge drinking.
- Moreover, there was a synergistic increase in liver-related events with weekly binge drinking in people with metabolic syndrome.

Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection

We searched Medline and Embase and included studies that enrolled HIV-monoinfected patients with NAFLD defined by imaging and/or liver histology. Data on prevalence and risk factors for NAFLD, NASH and fibrosis were collected for meta-analysis using random effects models.

- The prevalence of NAFLD (Imaging studies), NASH and fibrosis (biopsied populations) were 35% , 42% and 22%, respectively.
- High BMI, waist circumference, type 2 diabetes, hypertension, triglycerides and high $CD4^+$ cell count were associated with NAFLD, whereas HIV viral load, duration of HIV infection, duration of antiretroviral therapy and $CD4^+$ cell count nadir were not.

Miscellaneous

Liver Disease in Patients with Cardiac Disease

Congestive hepatopathy is progressive liver dysfunction resulting from chronic heart failure.

MELD-XI scores and liver histology may be used in conjunction to risk-stratify patients for cardiac transplantation.

After surgical repair of congenital cardiac abnormalities, sequelae of congestive hepatopathy include an increased risk for hepatocellular carcinoma.

Cardiac medications, including amiodarone and calcium-channel blockers, have been implicated in progressive liver dysfunction.

Liver Disease in Patients with Cardiac Disease

- **Major lesions**

Centrilobular congestion

Centrilobular sinusoidal dilatation

Hepatocyte atrophy

Perivenular/perisinusoidal fibrosis (“cardiac sclerosis”)

Periportal fibrosis

Bridging fibrosis (central-central; central-portal)

Periportal nodularity (regenerative hyperplasia)

Cirrhosis

- **Nodular lesions**

Nodular regenerative hyperplasia

Focal nodular hyperplasia-like

Hepatocellular adenoma-like

Hepatocellular carcinoma

Combined hepatocellular-cholangiocarcinoma

- **Other**

Steatosis; steatohepatitis

Glycogen nuclei

Extramedullary hematopoiesis

Gastroenterol Clin North Am. 2017 Jun;46(2):421-435.

GvHD

- Most biopsies 92% showed some features of GVHD. 10% had no GVHD, 39% had possible GVHD, and 52% had likely GVHD.
- Bile duct damage and intraepithelial lymphocytes were significantly more frequent in likely GVHD groups.
- Bile duct injury score calculated as the sum of bile duct damage and intraepithelial lymphocytes score.
- A bile duct injury score ≥4 correlated well with a diagnosis of GVHD, with sensitivity of74% and specificity 88%.
- Many cases 70.6% had a concurrent disease process: drug-induced liver injury 16% and sinusoidal obstruction syndrome 12% are particularly important causes of liver dysfunction.
- Moderate degree of bile duct injury and intraepithelial lymphocytes were the most helpful histology findings to confirm the diagnosis of GVHD.

Table 4 Disease processes identified histologically in 52 liver biopsies

Disease processes	No. of cases (%)
Drug-induced liver injury	11 (21.2%)
Siderosis, 4+	11 (21.2%)
Sinusoidal obstruction syndrome	6 (11.5%)
Steatosis (>33%)	4 (7.7%)
Steatohepatitis	3 (5.8%)
Extramedullary hematopoiesis	2 (3.8%)
Chronic hepatitis C	1 (1.9%)
Cholangitis lenta	1 (1.9%)

Hum Pathol. 2017 Aug;66:136-143

Table 3 Average scores of histologic features in no and possible GVHD group and likely GVHD group

	No GVHD, possible GVHD (N = 25)	Likely GVHD (N = 25)	*P*
Bile duct damage	1.48 ± 1.5	2.44 ± 0.70	.0003
Bile duct intraepithelial lymphocytes	0.83 ± 0.72	1.78 ± 0.70	.00001
Portal inflammation	0.76 ± 0.93	0.81 ± 0.79	.30
Lobular inflammation	0.64 ± 1.04	0.48 ± 0.70	.43
Ballooning	0.76 ± 0.93	0.59 ± 0.57	.040
Canalicular cholestasis	1.32 ± 1.38	1.04 ± 1.19	.24
Apoptosis	0.64 ± 0.81	0.93 ± 0.87	.10
Fibrosis [a]	5/25 (80.0%)	4/27 (14.8%)	.45
Siderosis	2.12 ± 1.42	2.44 ± 1.37	.20
Steatosis	0.48 ± 0.65	0.59 ± 0.64	.27
Ductpenia [a]	4/25 (16.0%)	3/27 (11.1%)	.46
Bile ductular proliferation [a]	12/25 (48.0%)	8/27 (29.6%)	.26
Endotheliitis [a]	1/25 (4.0%)	2/27 (7.4%)	.52
Hepatocytes necrosis [a]	6/25 (24.0%)	1/27 (3.7%)	.04
Sinusoidal dilatation [a]	4/25 (16.0%)	2/27 (7.4%)	.30

[a] Item was evaluated for presence or absence.

Bile duct damage

0 = Not Present

1 = <50% bile ducts, <1/2 circumference

2 = <50% bile ducts, >1/2 circumference or >50% bile ducts <1/2 circumference

3 = >50% bile ducts, >1/2 circumference

Bile duct intraepithelial lymphocytes

0 = Not Present

1 = One or more lymphocytes in one bile duct

2 = Lymphocytes in more than one bile duct

3 = Lymphocytes in all bile ducts

Not applicable due to complete ductopenia

The Good News

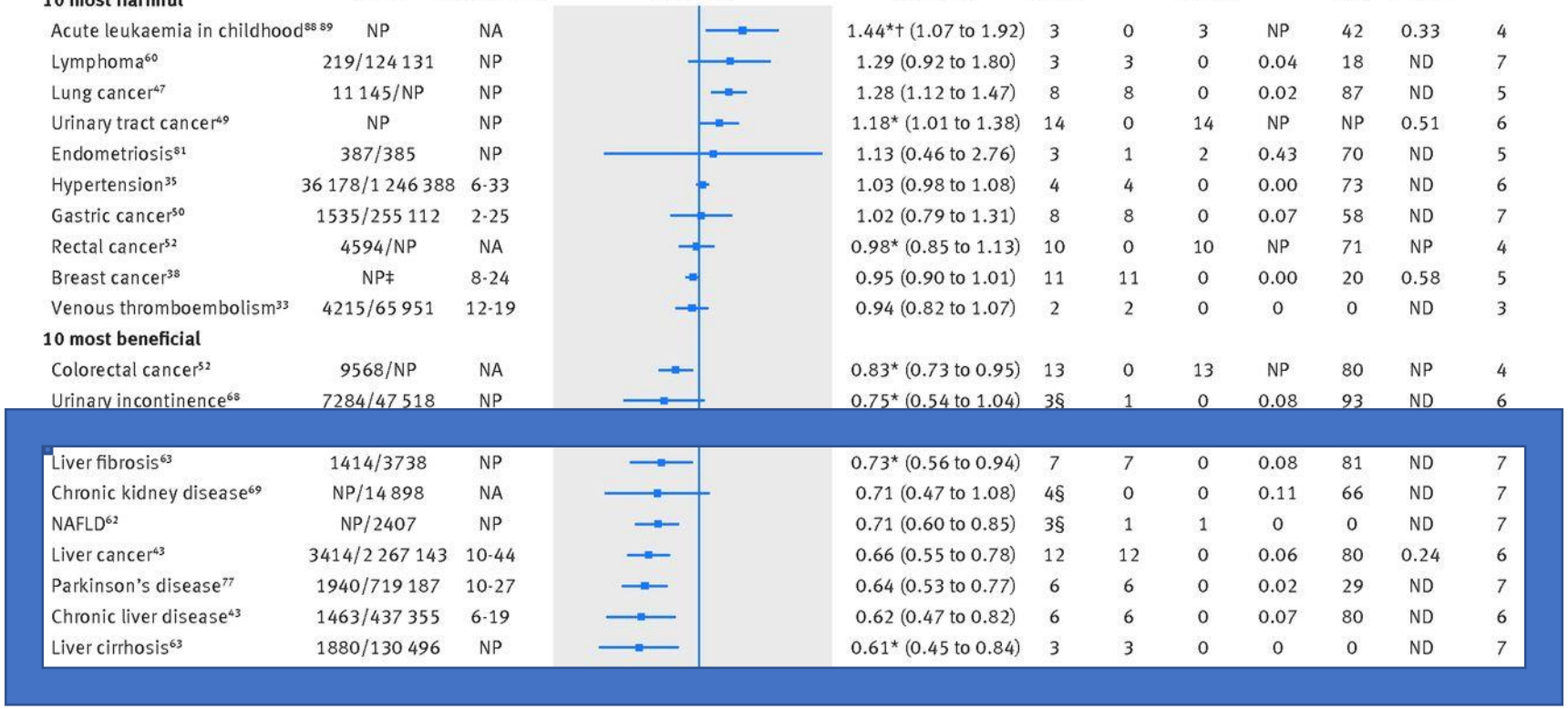
Beneficial Effects of Statins on the Rates of Hepatic Fibrosis, Hepatic Decompensation, and Mortality in Chronic Liver Disease

- Statins may improve outcomes in patients with chronic liver disease (CLD). We conducted a systematic review and meta-analysis to evaluate the impact of statins in the setting of CLD.
- Statins may retard the progression of hepatic fibrosis, may prevent hepatic decompensation in cirrhosis, and may reduce all-cause mortality in patients with CLD.
- As the quality (certainty) of evidence is low, further studies are needed before statins can be routinely recommended.

Coffee

- Polyphenols and caffeine in coffee have several well described hepato-protective properties, but coffee consumption has also been associated with a 14% risk reduction in all-cause mortality in the general population.
- Drinking three or more cups of coffee per day halved all-cause mortality risk in patients co-infected with HIV-HCV, and this association remained significant even after adjustment for relevant co-factors like severe liver fibrosis, and smoking status

Outcome	No of events /total	Follow-up range (years)	Risk estimate (95% CI)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
10 most harmful											
Acute leukaemia in childhood[88 89]	NP	NA		1.44*† (1.07 to 1.92)	3	0	3	NP	42	0.33	4
Lymphoma[60]	219/124 131	NP		1.29 (0.92 to 1.80)	3	3	0	0.04	18	ND	7
Lung cancer[47]	11 145/NP	NP		1.28 (1.12 to 1.47)	8	8	0	0.02	87	ND	5
Urinary tract cancer[49]	NP	NP		1.18* (1.01 to 1.38)	14	0	14	NP	NP	0.51	6
Endometriosis[81]	387/385	NP		1.13 (0.46 to 2.76)	3	1	2	0.43	70	ND	5
Hypertension[35]	36 178/1 246 388	6-33		1.03 (0.98 to 1.08)	4	4	0	0.00	73	ND	6
Gastric cancer[50]	1535/255 112	2-25		1.02 (0.79 to 1.31)	8	8	0	0.07	58	ND	7
Rectal cancer[52]	4594/NP	NA		0.98* (0.85 to 1.13)	10	0	10	NP	71	NP	4
Breast cancer[38]	NP‡	8-24		0.95 (0.90 to 1.01)	11	11	0	0.00	20	0.58	5
Venous thromboembolism[33]	4215/65 951	12-19		0.94 (0.82 to 1.07)	2	2	0	0	0	ND	3
10 most beneficial											
Colorectal cancer[52]	9568/NP	NA		0.83* (0.73 to 0.95)	13	0	13	NP	80	NP	4
Urinary incontinence[68]	7284/47 518	NP		0.75* (0.54 to 1.04)	3§	1	0	0.08	93	ND	6
Liver fibrosis[63]	1414/3738	NP		0.73* (0.56 to 0.94)	7	7	0	0.08	81	ND	7
Chronic kidney disease[69]	NP/14 898	NA		0.71 (0.47 to 1.08)	4§	0	0	0.11	66	ND	7
NAFLD[62]	NP/2407	NP		0.71 (0.60 to 0.85)	3§	1	1	0	0	ND	7
Liver cancer[43]	3414/2 267 143	10-44		0.66 (0.55 to 0.78)	12	12	0	0.06	80	0.24	6
Parkinson's disease[77]	1940/719 187	10-27		0.64 (0.53 to 0.77)	6	6	0	0.02	29	ND	7
Chronic liver disease[43]	1463/437 355	6-19		0.62 (0.47 to 0.82)	6	6	0	0.07	80	ND	6
Liver cirrhosis[63]	1880/130 496	NP		0.61* (0.45 to 0.84)	3	3	0	0	0	ND	7



NP=not published; NA=not appropriate;
ND=not done; NAFLD=non-alcoholic fatty liver disease
*Summary measure expressed as odds ratio in original meta-analysis article
†Fixed effects model
‡Could not be separated from other outcomes
§Included cross sectional studies

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