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REVIEW

Current updates in HCC screening and treatment

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Primary liver cancer is the seventh most common cause of new cancer diagnoses worldwide but remains the third most common cause of cancer-related death.[1] HCC accounts for 75%–85% of liver cancer diagnoses and is projected to be the third leading cause of cancer-related death in the United States by 2035, surpassing colorectal cancer.[2,3] Due to the high incidence and subsequent mortality of HCC, appropriate screening and prompt treatment are essential. Here we aim to provide an overview of the existing landscape of HCC screening and current and emerging treatment options.

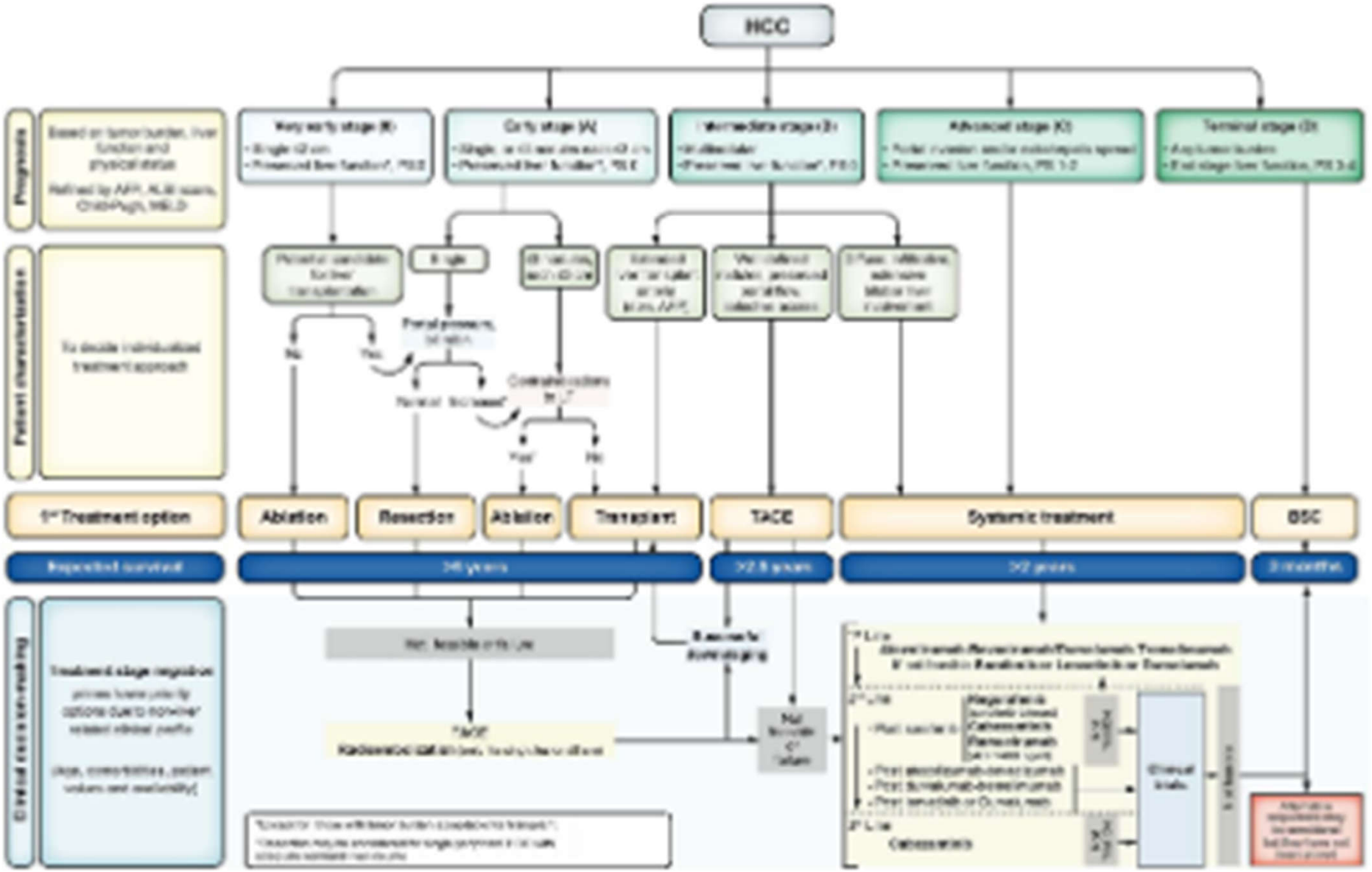

FIGURE 1 BCLC staging system for the treatment of HCC. Reprinted with permission from Reig M, Forner A, Rimola J, Ferrer-Fábrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022; 76:681–93. © 2021 European Association for the Study of the Liver. Published by Elsevier B.V.[20] Abbreviation: BCLC, Barcelona Clinic Liver Cancer.

patients (≤3 tumors up to 3 cm in size).[11,12] Both radio- arm after curative resection had significantly better

TABLE 2 Summary of recent trial data for systemic therapy options for HCC

Study	Outcome	Drugs investigated	Median OS, months (95% CI)	HR for death (95% CI)	Median PFS, mor (95% CI)
Imbrave 150[52]	Positive for overall survival	Atezolizumab + Bevacizumab	19.2 (17.0–23.7)	0.66 (0.52–0.85)	6.9 (5.7–8.6)
	—	Sorafenib	13.4 (11.4–16.9)	—	4.3 (4.0–5.6)
HIMALAYA[42]	Positive for overall survival	Durvalumab + Tremelimumab	16.4 (14.2–19.6)	0.78 (96.02 CI: 0.65–0.93)	3.8 (3.7–5.3)
	—	Sorafenib	13.8 (12.3–16.1)	—	4.1 (3.8–5.5)
RESCUE[43]	First-line	Camrelizumab + Apatinib	–	–	5.7 (5.4–7.4)
	second-line	—	–	—	5.5 (3.7–5.6)
SHR-1210-III-310[54]	Positive for overall survival	Camrelizumab + Rivoceranib	22.1 (19.1–27.2)	0.62 (0.49–0.80)	5.6 (5.5–6.3)
	—	Sorafenib	15.2 (13.0–18.5)	—	3.7 (2.8–3.7)
COSMIC-312[55]	Positive for progression-free survival	Cabozantibinib + Atezolizumab	15.4 (96 CI: 13.7–17.7)	0.9 (96 CI: 0.69–1.18)	6.8 (99 CI: 5.6–8
	—	Sorafenib	15.5 (96 CI: 12.1–Not estimable)	—	4.2 (99 CI: 2.8–7
LEAP-002[56]	Negative	Lenvatinib + Pembrolizumab	21.2 (19.0–23.6)	0.84 (0.71–1.0)	8.2 (6.3–8.3)
	—	Lenvatinib	19.0 (17.2–21.7)	—	8.1 (6.3–8.3)

Future directions

There have been remarkable advances in treatment options for HCC in the last several years, which have been unparalleled. A major shift in first-line systemic therapy has occurred with the use of combination therapy and immunotherapy, yielding overall survival rates that had not been previously seen (Table 2). Although immunotherapy in HCC is only effective in 20%–30% of patients, those who respond to immunotherapy have durable response rates. The development of biomarkers to guide treatment response will be essential to enhancing therapeutic options. We anticipate future studies to address the potential synergistic effects of locoregional therapy with immunotherapy combinations, immunotherapy in the adjuvant and neoadjuvant space, and to enhance treatment options for difficult-to-treat patient populations, including liver transplant recipients and those who fail first-line options.

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MINIREVIEWS

Value of cardiac magnetic resonance on the risk stratification of cardiomyopathies

Rafael Vidal-Perez, Mariana Brandão, Wael Zaher, Ruben Casado-Arroyo, Alberto Bouzas-Mosquera, Ricardo Fontes-Carvalho, Jose Manuel Vazquez-Rodriguez

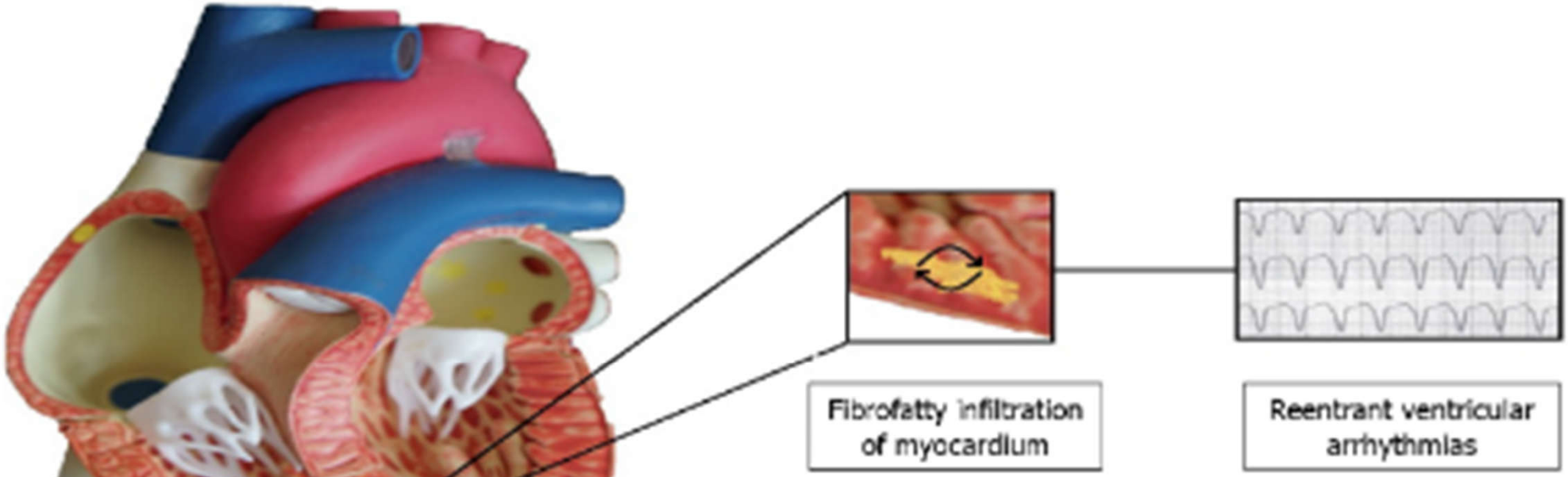
Abstract

Cardiomyopathies represent a diverse group of heart muscle diseases with varying etiologies, presenting a diagnostic challenge due to their heterogeneous manifestations. Regular evaluation using cardiac imaging techniques is imperative as symptoms can evolve over time. These imaging approaches are pivotal for accurate diagnosis, treatment planning, and optimizing prognostic outcomes. Among these, cardiovascular magnetic resonance (CMR) stands out for its ability to provide precise anatomical and functional assessments. This manuscript explores the significant contributions of CMR in the diagnosis and management of patients with cardiomyopathies, with special attention to risk stratification. CMR's high spatial resolution and tissue characterization capabilities enable early detection and differentiation of various cardiomyopathy subtypes. Additionally, it offers valuable insights into myocardial fibrosis, tissue viability, and left ventricular function, crucial parameters for risk stratification and predicting adverse cardiac events. By integrating CMR into clinical practice, clinicians can tailor

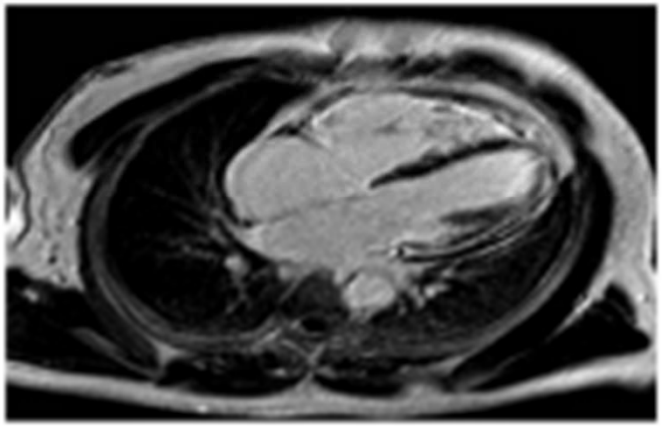
patient-specific treatment plans, implement timely interventions, and optimize long-term prognosis. The non-invasive nature of CMR reduces the need for invasive procedures, minimizing patient discomfort. This review highlights the vital role of CMR in monitoring disease progression, guiding treatment decisions, and identifying potential complications in patients with cardiomyopathies. The utilization of CMR has significantly advanced our understanding and management of these complex cardiac conditions, leading to improved patient outcomes and a more personalized approach to care.

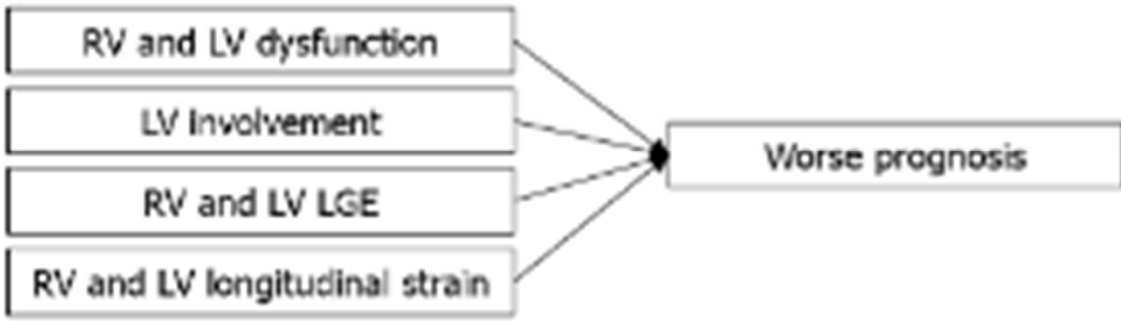
Key Words: Cardiac magnetic resonance; Cardiomyopathies; Prognosis; Dilated cardiomyopathy; Hypertrophic cardiomyo-

Ventricular arrhythmia substrate in arrhythmogenic cardiomyopathy



CMR correlation





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CONCLUSION

Cardiovascular imaging methods play a vital role in investigating cardiomyopathies, furnishing valuable diagnostic and prognostic insights. The inclusion of CMR in the evaluation of all patients is highly recommended, owing to its ability to offer comprehensive anatomical, functional, and tissue-specific data, which holds significant prognostic value. While other imaging techniques might be employed selectively, the integration of multiple modalities of cardiac imaging assumes a crucial role in clinical decision-making, leading to enhanced patient management and care outcomes.

Core Tip: Cardiomyopathies encompass a diverse range of diseases affecting the heart muscle, each with varied causes. Symptoms of cardiomyopathies can manifest differently and change over time, necessitating regular evaluation through cardiac imaging techniques. These approaches play a crucial role in diagnosis, treatment guidance, and prognosis optimization. To enhance the precision of anatomical and functional evaluation and obtain valuable prognostic insights, cardiovascular magnetic resonance (CMR) is typically employed. By integrating CMR into clinical practice, clinicians can tailor patient-specific treatment plans, implement timely interventions, and optimize long-term prognosis This manuscript aims to explore how the CMR contribute to the diagnosis and management of patients with cardiomyopathies specially focus on the risk stratification.

COMMENTARY

Optimal Prescribing of Statins to Reduce Cardiovascular Disease

Cardiovascular disease is the most common cause of death in the United States and worldwide. Most of this disease is preventable with improvement of lifestyle and medication to reduce circulating cholesterol. The most common medications prescribed to reduce cholesterol are statins, which inhibit the hepatic enzyme HMG-CoA reductase, the limiting enzyme in cholesterol synthesis. Unfortunately, statins are rarely prescribed correctly, resulting in excessive adverse events and very poor patient compliance. In fact, studies have demonstrated that approximately 50% of patients prescribed statins are no longer taking the medication within 1 year of obtaining a prescription.[1] This omission results in less than half of all "at risk" patients achieving national guideline low-density lipoprotein (LDL) cholesterol goals, thereby resulting in excessive cardiovascular mortality.

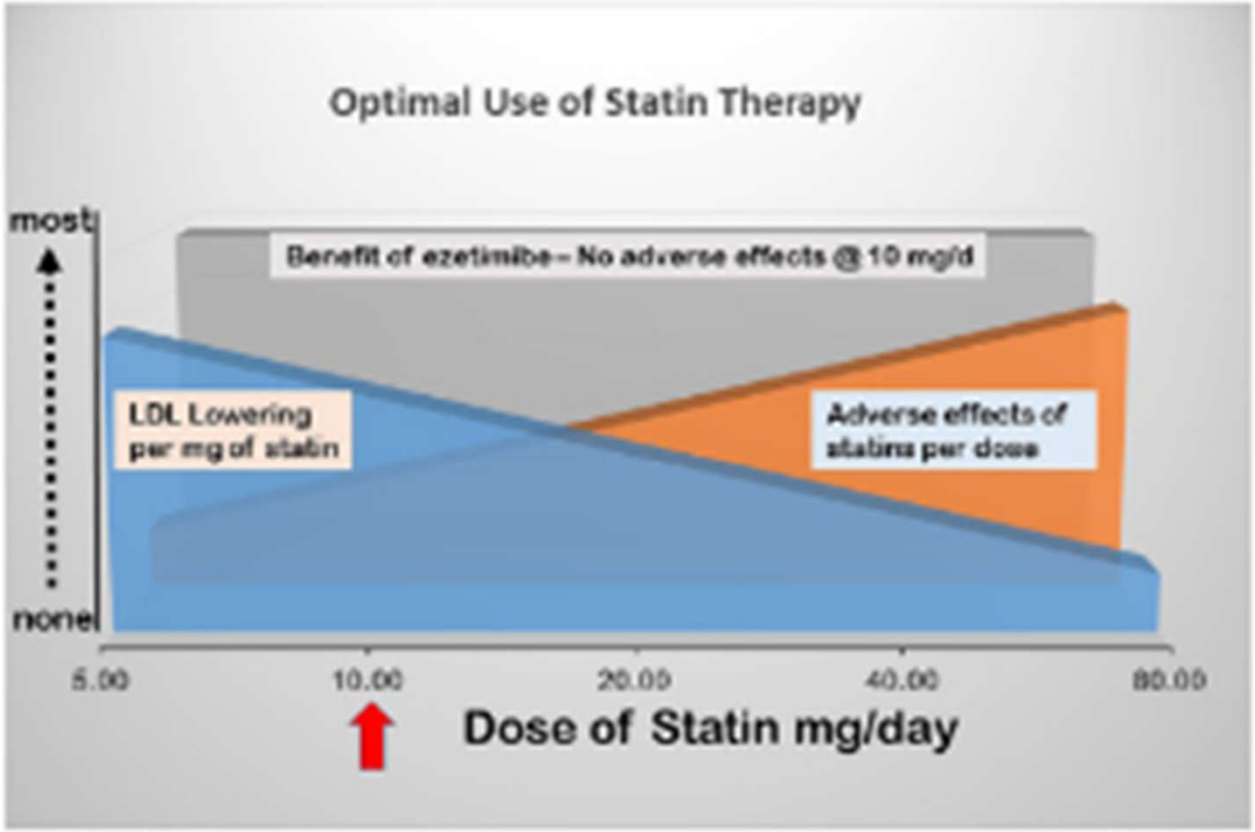

Figure A schematic diagram demonstrating that the adverse effects of statins are dose dependent, whereas the effectiveness of statins in lowering low-density lipoprotein (LDL) cholesterol per milligram of drug is the opposite. Ten milligrams of rosuvastatin/day (arrow) achieves a reasonable balance between adverse effects and LDL lowering. The addition of ezetimibe adds significantly to the LDL-lowering and anti-inflammatory effects of statins without additional adverse effects.

In summary, physicians should optimize the use of statins by considering the fact that the adverse effects are dose related, but the potency in lowering LDL cholesterol is not (Figure). In addition, statins, which don't compete with the metabolism of other medications, should be utilized. Based on physiology, in the majority of "at risk" patients, 10 mg of rosuvastatin plus 10 mg/d of ezetimibe are a logical initial choice to optimize statin use.

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Research Article

Gamma-Glutamyl Transferase: A Friend against Cholestatic Itch? A Retrospective Observational Data Analysis in Patients with Extrahepatic Cholestasis

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Background and Aim of This Study. Itch frequently occurs in patients with chronic cholestasis. However, it remains unclear why some patients do and others do not develop pruritus. In addition, drug treatment is frequently ineffective. We repeatedly observed that cholestatic patients without itch had a relatively high serum gamma-glutamyl transpeptidase (GGT), relative to their serum bilirubin. The aim of this study was to validate this clinical observation. *Methods*. We included 235 patients with chronic extrahepatic cholestasis due to pancreatic cancer, cholangiocarcinoma, or papillary carcinoma. *Results*. GGT was significantly higher in patients without pruritus (median 967, IQR 587–1571) compared to patients with pruritus (median 561 IQR 266–1084 IU/l) ($p < 0.01$). In contrast, median alkaline phosphatase (AP) was 491 U/L (IQR; 353–684) in patients with pruritus and was not significantly different from 518 U/L (IQR; 353–726) in patients without pruritus ($p = 0.524$). Direct bilirubin was significantly higher in patients with pruritus compared to patients without pruritus (168 μmol/L (IQR; 95–256) vs. 120 μmol/L (IQR; 56.75–185.5)) ($p < 0.01$). After correcting for the extent of cholestasis *via* direct bilirubin, the negative association between GGT and pruritus remained significant and became stronger ($p < 0.001$). *Conclusion*. Serum GGT activity is inversely associated with the presence of cholestatic itch in patients with chronic extrahepatic cholestasis.

5. In Conclusion

The present study shows a strong negative association between serum GGT activity and the presence of itch in cholestatic patients.

The main question that rises from our results is whether this is a causal relationship or not. Therefore, our future perspective is to test GGT administration in an animal model of cholestatic itch.

Pathogenesis of primary liver carcinomas

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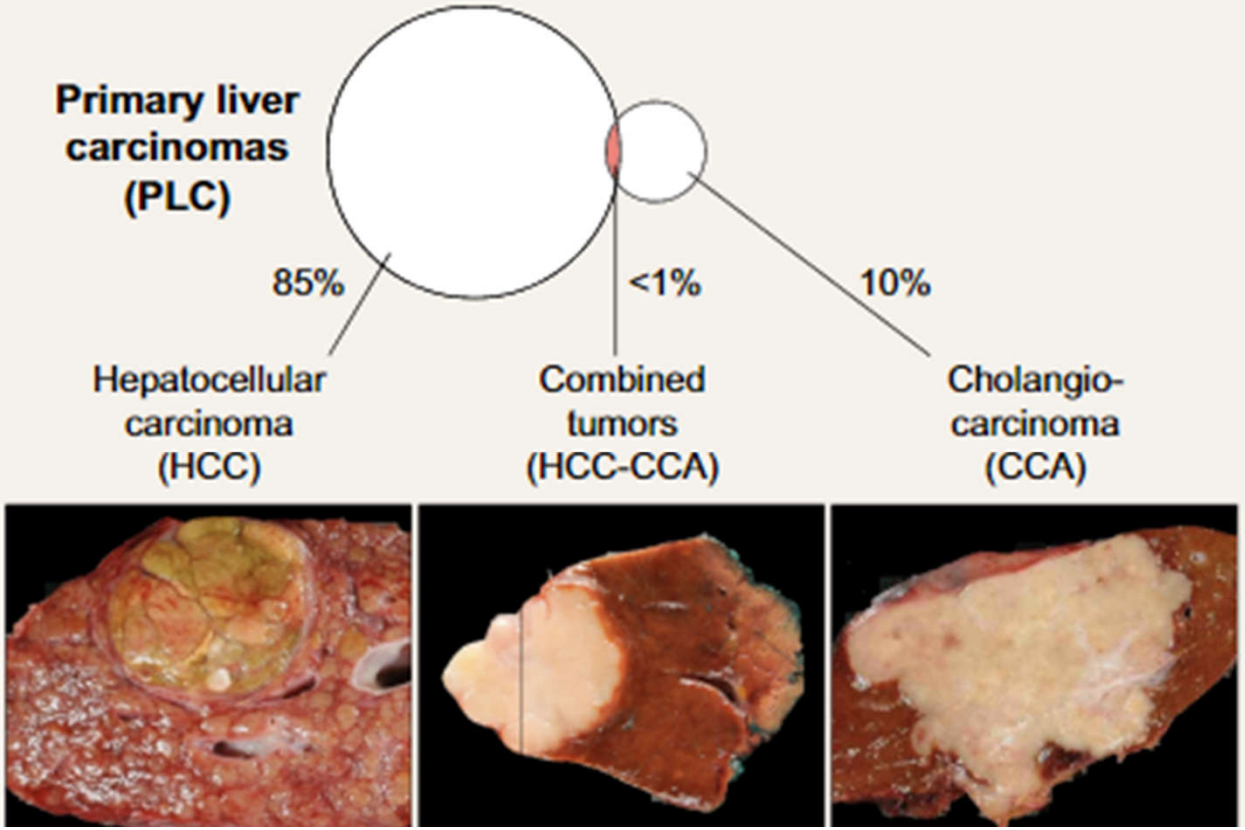

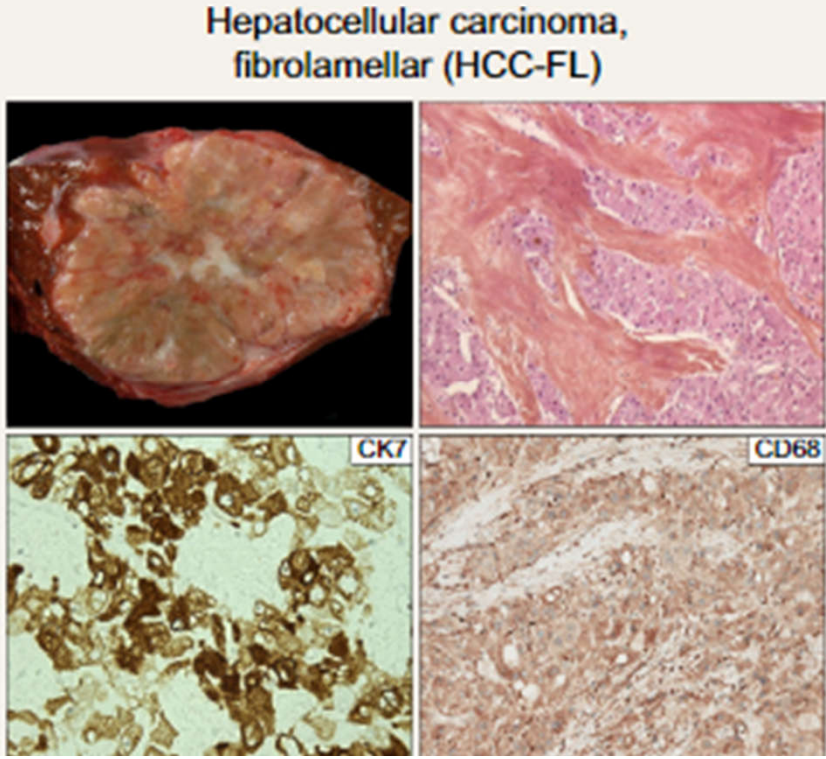

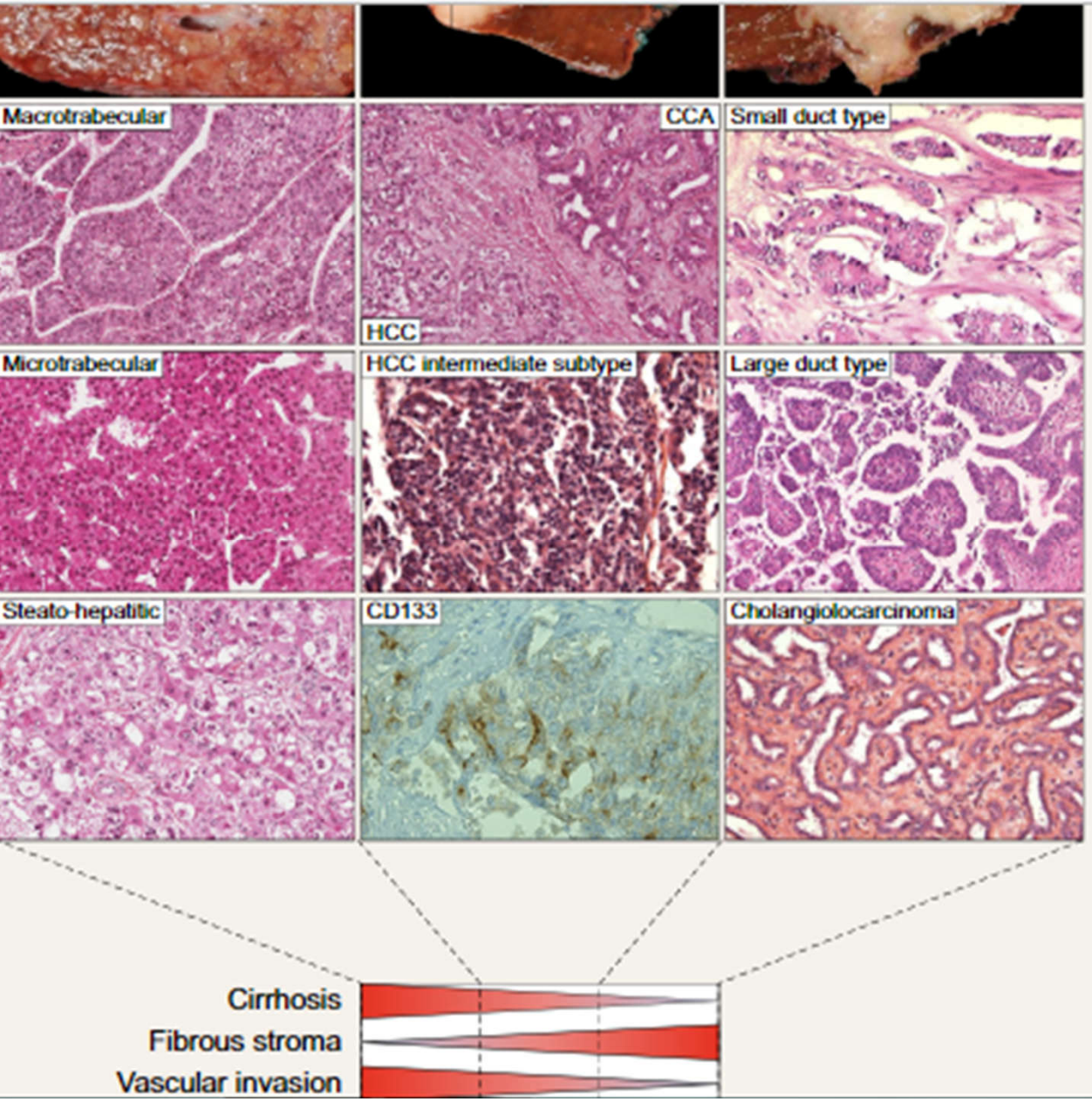

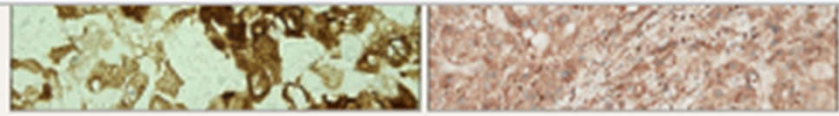

Main hallmark features of PLC

Clinics	Features	HCC	HCC-CCA	iCCA	HCC-FL
Risk factors	Viruses HBC/HCV				
	Cysts and stones				
	Alcohol				
	Metabolic syndrome				
Liver pathology	**Features**				
Non-tumoral liver	Cirrhosis				
	NASH				
Tumor	Hypervascular				
	Fibrous stroma				
	Vascular invasion				
Diagnostic markers	**Proteins**				
IHC markers	Glypican 3				
	HepPar1				
	CK7				
	EpCAM				
	CK19				
	Stem cell				
	CD68				
Pathways	**Gene alterations**				
Telomere maintenance	*TERT* promoter				
WNT/β-catenin	*CTNNB1*				
	AXIN1				
Cell cycle Survival	*PTS3*				
	RB1				
	*IDH1/2**				
Chromatin remodelling	*ARID1A*				
	BAP1				
RAS signalling	*KRAS*				
	*BRAF**				
	RPS6KA3				
Growth factor signalling	*FGFR2* fusion*				
	FGF19 amplification*				
	MET amplification*				
	HER2 amplification*				

Primary liver cancer (PLC) is the third leading cause of cancer death, accounting for 830,180 deaths worldwide in 2020. PLCs are mainly composed of hepatocellular carcinoma (HCC, ~85%) and intrahepatic cholangiocarcinoma (iCCA, ~10%).[1] HCC is PLC characterized by hepatocellular differentiation; in contrast, CCAs are biliary differentiated tumors. HCC and iCCA define a spectrum of PLCs that also include mixed tumors (combined HCC-CCA [cHCC-CCA]), which are much more uncommon (~1%). They are defined by the presence of HCC and CCA areas in various proportions, as well as, in some cases, the presence of transitional features within the same tumor.[2,3]

HCC and iCCA are unique in terms of epidemiology and risk factors. While HCC mostly develops in males in the context of chronic liver diseases and cirrhosis, iCCA usually arise in the absence of underlying liver fibrosis. Usual risk factors for HCC include HCV and HBV infections, excessive alcohol intake, and non-alcoholic fatty liver disease. Cysts and stones are specifically associated with iCCA.[4] In between, cHCC-CCA develop more often than iCCA in patients with advanced fibrosis and cirrhosis (in approximately 50% of cases).[5] Morphologically, in addition to the specific aspect of cell proliferation (hepatocyte *vs.* cholangiocyte), PLCs display some hallmark features that enable their differential recognition, including the desmoplastic fibrous stroma and perineural infiltration in iCCA, or the presence of bile plugs or steatosis and vascular invasion in HCC.

At the molecular level, most of the genomic alterations identified in HCC are also found in cHCC-CCA and iCCA but at different frequencies. Overall, cHCC-CCAs more closely resemble HCC than iCCA.[6] However, some genomic alterations, *CTNNB1* mutations), in iCAA (*FGF* amplifications/fusion genes, *KRAS*, *BRAF*, and *IDH1/2* mutations) and only in a few cases of cHCC-CCA.[7] Interestingly, specific molecular alterations in both HCC and iCCA are correlated with morphological subtypes. *TP53* and *CTNNB1* alterations are associated with macrotrabecular/massive and microtrabecular/pseudoglandular HCC, respectively, showing prognostic relevance.[8] Similarly, small- and large-duct iCCAs display specific gene alterations including *IDH1/2* mutations and *FGFR2* fusions, and *SMAD4* and *MDM2* mutations, respectively.[9] Usually, cHCC-CCAs show a liver progenitor cell phenotype with CK19, CD133 and CD56 expression. Also, among HCCs, a subtype of tumors show a progenitor phenotype and are less differentiated.

Among PLCs, fibrolamellar carcinomas (FLCs) define a specific subgroup of HCC with specific clinical features: young age with occurrence between 10 to 35 years, a balanced sex ratio and no chronic liver disease. Also, prognosis is better, with 80% survival 5 years after resection.

In addition, FLCs show a specific stage of differentiation with co-expression of hepatocellular (HEPPAR1), biliary (CK7), macrophage (CD68), and neuroectodermic markers.[10] Molecular features in FLC contrast with all other PLCs with the presence of the *DNAJB1-PRKACA* fusion gene exclusively observed in FLC, in the absence of other genes classically mutated in HCC and CCA. Interestingly, BAP1-mutated HCCs show frequent heterogeneous mixed FLC-HCC histology, illustrating the continuum between tumor subgroups and specific stage of differentiation and/or cell at the origin of the malignant transformation.

THE END