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Beyond bones: Revisiting the role of vitamin D in chronic liver disease



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Abstract

Beyond its traditional role in calcium and bone metabolism, vitamin D has emerged as a critical regulator of liver health. Its active form, calcitriol [$1\alpha,25(\text{OH})_2\text{D}$], signals through the vitamin D receptor (VDR), which is expressed in hepatic stellate cells, Kupffer cells, and cholangiocytes. Through this pathway, vitamin D modulates fibrosis, inflammation, oxidative stress, bile acid homeostasis, and immune responses. This review explores the growing body of evidence linking vitamin D deficiency to chronic liver diseases, including autoimmune hepatitis, primary biliary cholangitis, alcoholic liver disease, viral hepatitis B and C, and metabolic-associated steatotic liver disease. Low vitamin D levels are frequently observed in these conditions and are associated with disease severity, complications (such as spontaneous bacterial peritonitis, sarcopenia, and hepatic encephalopathy), and increased mortality. Mechanistically, vitamin D-VDR signaling inhibits profibrotic TGF- β 1/SMAD pathways, downregulates proinflammatory cytokines, enhances regulatory T cell differentiation, and improves insulin sensitivity. Although preclinical studies support its protective effects, clinical trials of vitamin D supplementation have produced mixed results. Overall, vitamin D appears to influence multiple pathways in liver disease pathophysiology, and correcting its deficiency may offer clinical benefits. However, its integration into clinical care will depend on identifying responsive patient subgroups and defining optimal dosing strategies to maximize therapeutic benefit.

Core Tip: Vitamin D plays diverse roles in chronic liver disease beyond bone health, including modulation of fibrosis, immune responses, bile acid metabolism, and oxidative stress *via* vitamin D receptor signaling. Deficiency is common across liver disease etiologies and linked to worse outcomes. Although preclinical data are promising, clinical trials have yielded inconsistent results. This review summarizes the mechanistic and clinical evidence for vitamin D in autoimmune, viral, alcoholic, and metabolic liver diseases, emphasizing its potential as a modifiable factor and the need to define patient subgroups most likely to benefit from supplementation.

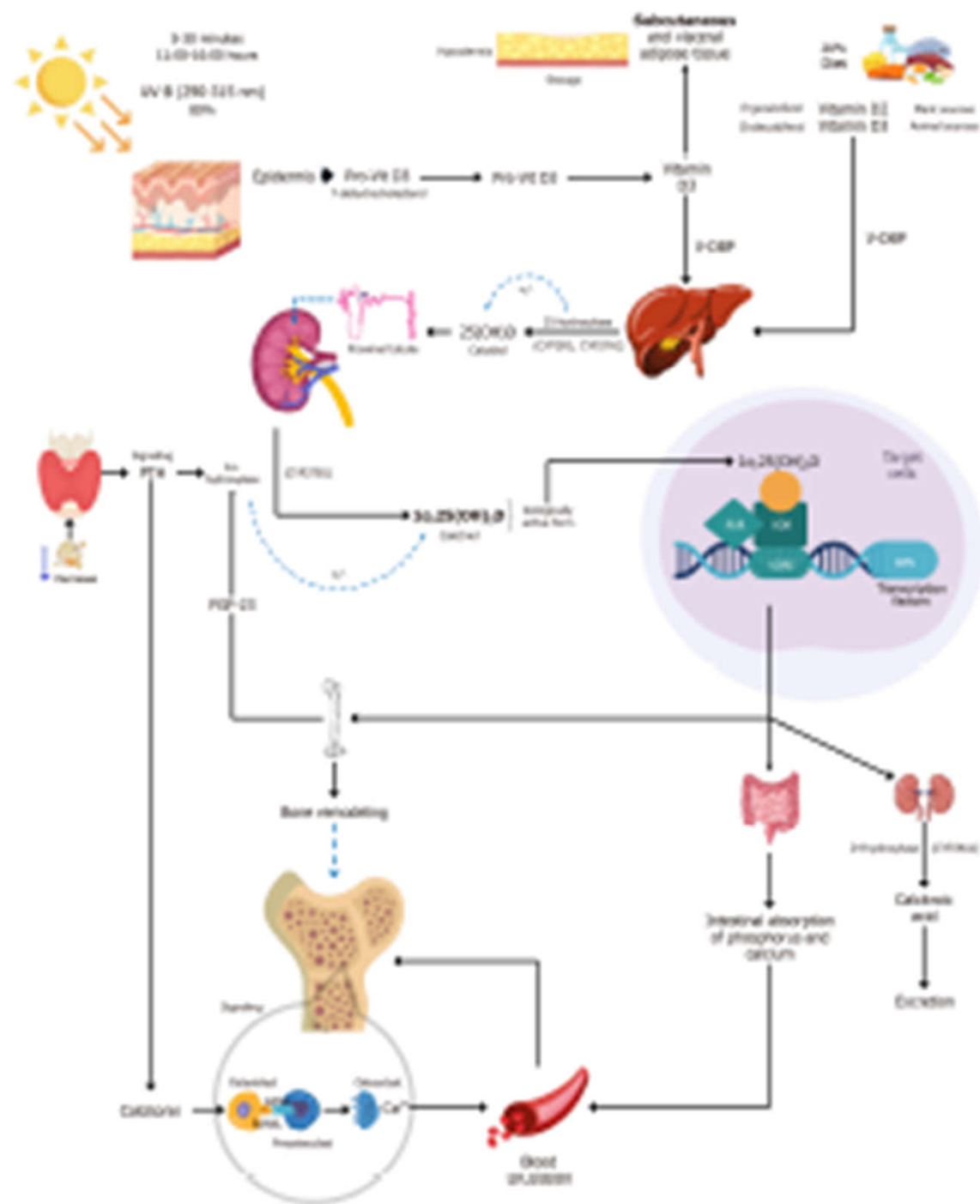


Figure 1 An integrated view of vitamin D metabolism. UVB: Ultraviolet B, VDBP: Vitamin D-binding protein, VDR: Vitamin D receptor, RXR: Retinoid X-receptor, VDRE: Vitamin D-response element, PTH: Parathyroid hormone, CYP27B1: CYP27B1 (Cytochrome P450 27B1).

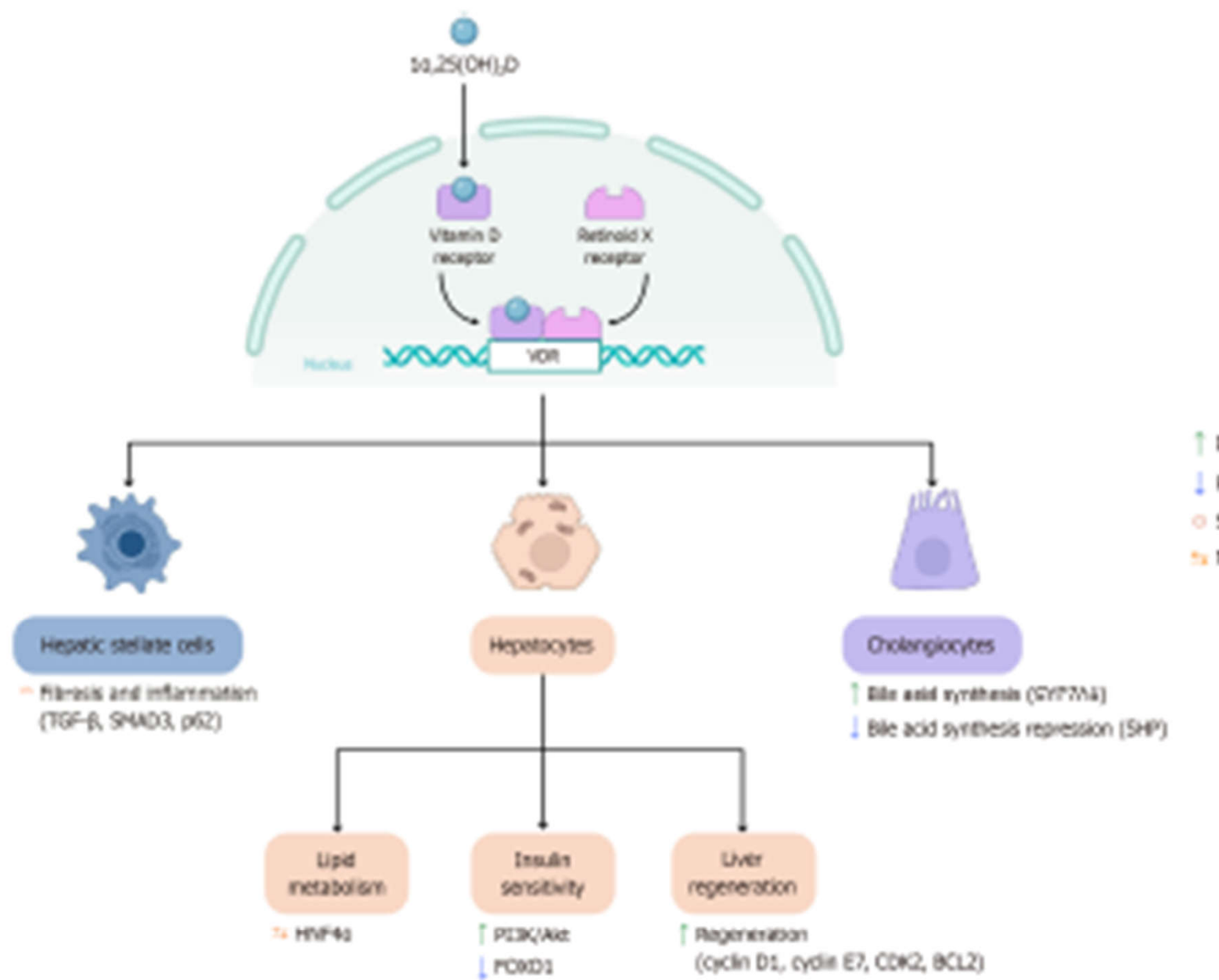


Figure 3 Vitamin D receptor signals in liver cell populations. VDR: Vitamin D receptor. Created in BioRender (Supplementary material).

VITAMIN D AND ITS RELATIONSHIP WITH CHRONIC LIVER DISEASES

Autoimmune liver disease

Vitamin D deficiency is a common finding not only in non-hepatic autoimmune diseases such as type 1 diabetes

High Steatosis-Associated Fibrosis Estimator scores predict hepatocellular carcinoma in viral and non-viral hepatitis and metabolic dysfunction-associated steatotic liver disease

Tung-Hung Su^{1,2}, Sheng-Shun Yang^{3,4,*}, Mei-Hsuan Lee^{5,*}, Wei-Yu Kao^{6,7}, Shang-Chin Huang^{8,9}, Fen-Fang Chen¹, Francis SK Poon³, Lung-Wen Tsai⁶, Yi-Ting Chen⁵, Che Lin¹⁰, Weichung Wang¹¹, W Ray Kim¹², and Jia-Horng Kao^{1,2,9}

High SAFE scores (≥ 100) predict hepatocellular carcinoma with viral and non-viral hepatitis and metabolic dysfunction associated steatotic liver disease

DO WE HAVE HCC PREDICTORS USING ROUTINE PARAMETERS FOR CHRONIC LIVER DISEASES?



NTUH Cohort
12,963
CLD patients

HBV	5,449	NAFLD	1,575
HCV	1,819	ArLD	324
HBV/HCV	433	Other LC	433
MASLD	2,958	Other CLD	2,930

External Validations

Hospital cohort (Taichung VGH)

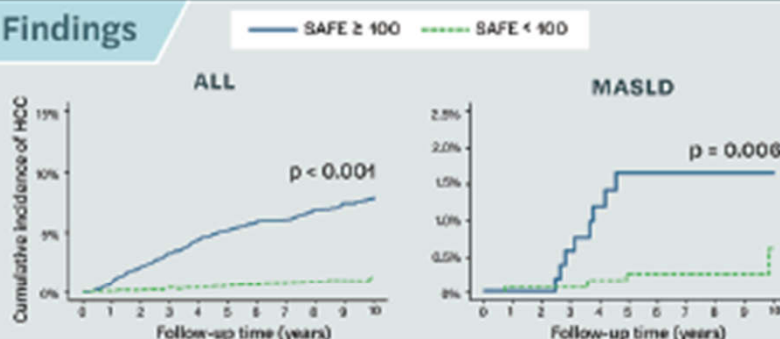
CLD	8,103
MASLD	2,643

Community cohort

MASLD	120,166
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Key Findings

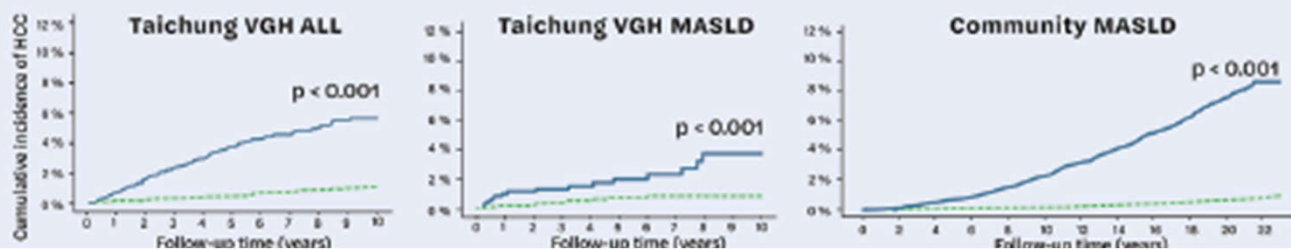
NTUH Cohort



Multivariable analyses using SAFE score (≥ 100 vs < 100) to predict HCC in various subgroups of chronic liver diseases

	Adjusted SHR	95% CI	P-Value
ALL	7.54	5.38-10.60	< 0.001
HBV	4.94	3.24-7.51	< 0.001
HCV	8.22	3.61-18.70	< 0.001
HBV/HCV	10.10	1.37-75	0.023
MASLD	4.23	1.43-12.50	0.009
Non-viral hepatitis	11.10	3.97-31.30	< 0.001
ArLD	8.07	0.93-69.90	0.058
Other LC	3.17	0.83-12.10	0.091
Other CLD	9.67	0.48-195	0.140

External Validations



Study Highlights

- The SAFE score consists of age, BMI, diabetes, AST, ALT, platelet, and globulin and can be used to predict the development of HCC regardless of etiologies of liver diseases.
- Patients with chronic liver diseases with a SAFE score (≥ 100) increase 7.5-fold risk of HCC compared with those with a SAFE score < 100 .
- A SAFE score (≥ 100) increases 4.2-fold risk of HCC in patients with MASLD and is validated in hospital and community cohorts.
- The SAFE score may be used as a universal HCC risk predictor to guide HCC surveillance.

with high FIB-4 levels for fibrosis evaluation. The SAFE score has recently outperformed other laboratory-based, non-invasive liver fibrosis tests, such as FIB-4.³⁰

We demonstrated that the SAFE score could predict HCC independent of the etiology of CLD. The SAFE score may serve as an HCC predictor for MASLD and ArLD, which currently do not have their HCC risk predictors.¹ We also found that the risk of HCC of MASLD is higher than

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MINIREVIEWS

Early screening for liver cancer must be performed

Zi-Han Liu, Wen-Jun Wang, Shuang-Suo Dang

Abstract

Hepatocellular carcinoma (HCC) is imposing a growing global health burden, with China accounting for nearly half of incident cases and mortality worldwide. Early screening is critical to improving survival in high-burden regions. However, the global standardized screening rate for high-risk populations is less than 24%, and HCC screening currently faces severe challenges. We synthesize recent advances in HCC screening, including optimized serum biomarkers, evolving imaging techniques, and validated models. Emerging liquid biopsy technologies and artificial intelligence further demonstrate considerable promise for enhancing noninvasive detection efficacy. Multifaceted collaboration among policymakers, healthcare systems, and communities is essential to implement effective screening programs and ultimately improve survival outcomes.

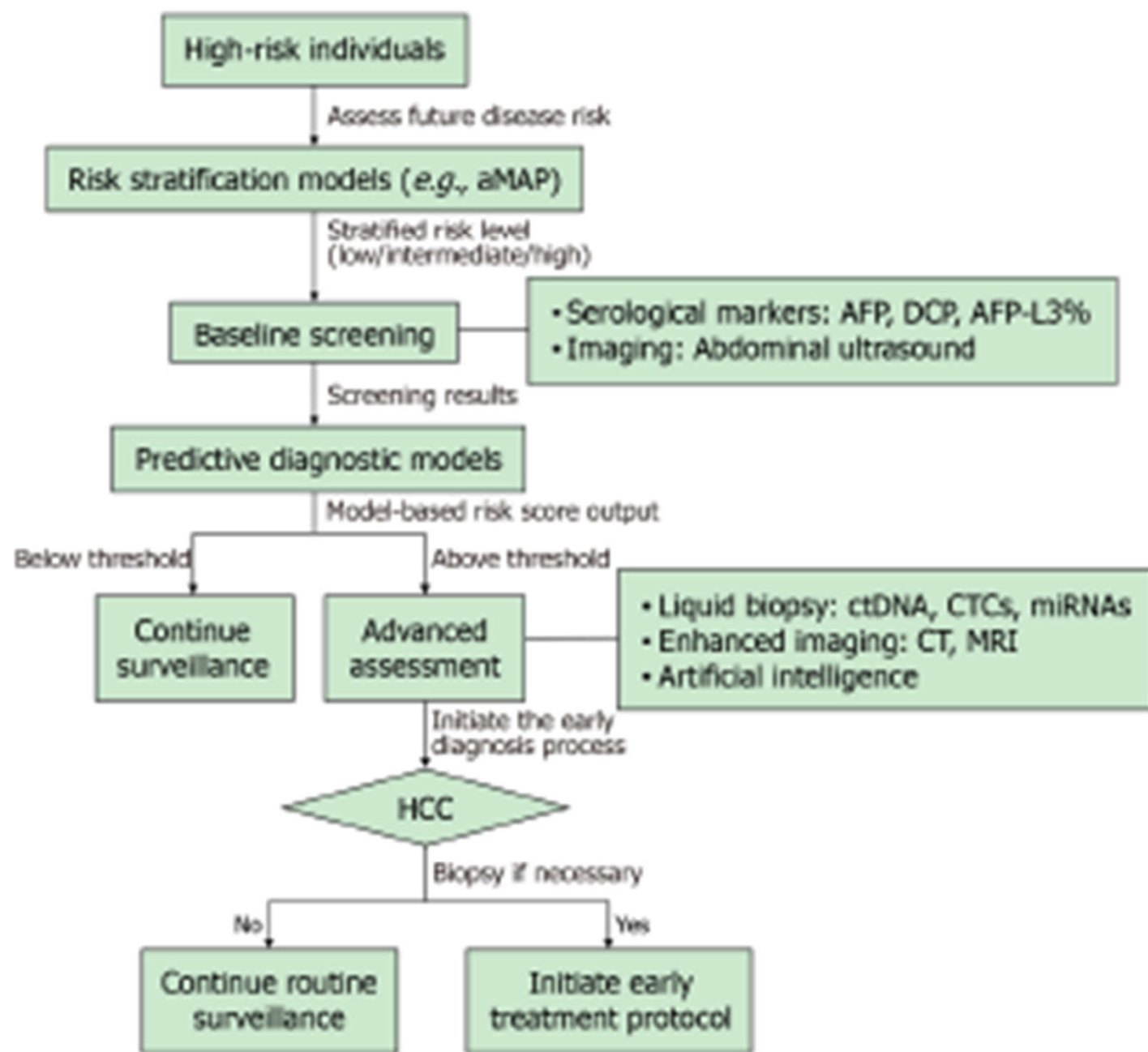


Figure 1 Clinical pathway for the integrated management of early hepatocellular

Core Tip: Hepatocellular carcinoma imposes a significant disease burden globally, particularly in China, where early screening faces challenges of low screening rates and insufficient sensitivity of traditional methods. This review focuses on the potential of innovative strategies, including optimized combinations of serum biomarkers, advanced imaging techniques, and liquid biopsy, to enhance early diagnosis rates. We emphasize the need for multidisciplinary collaboration and risk stratification management to improve screening efficacy.

AI ultrasound tool could reduce unnecessary biopsies by 60%



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An AI-based decision support tool could reduce unnecessary biopsies of benign breast lesions by about 60%, according to research presented December 4 at RSNA 2025.

In his talk, Michael Fishman, MD, from Mass General Brigham and Harvard Medical School in Boston, MA, shared results from his team's findings showing that the AI tool for breast ultrasound maintained high sensitivity for detecting malignancies while identifying benign lesions.

Expert panel develops new breast biopsy guidelines

A group of breast imaging experts has developed a set of recommendations to help guide providers in navigating breast biopsy decisions.


Published this week in *Insights Into Imaging*, the recommendations are the result of a collaboration between eight breast health experts from around the world. The team developed the guidelines to help providers effectively choose between the numerous minimally invasive diagnostic options for breast biopsy in multiple clinical scenarios.

“Although every practitioner of breast biopsies should be aware of the advantages and limitations of biopsy and imaging techniques, evidence-based literature discussing which biopsy technique and imaging combination is to be preferred for the diagnosis of breast lesions is sparse, and a general consensus is not available,” Wendelien B. G. Sanderink, MD, with the department of medical imaging at Radboud University Medical Center in the Netherlands, and colleagues noted. “This article provides an expert consensus for biopsy of breast lesions and re-biopsy in case of radiological-pathological

Image-guided biopsy of breast lesions—when to use what biopsy technique: the United States and Canadian perspective

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