

Annals of Gastroenterology and Digestive Disorders

Review Article

Open Access

Ultrasound and Biomarker-Based Surveillance for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection: A Review

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Received: 18 February 2025; Accepted: 7 May 2025; Published: 12 August 2025

Volume: 8; Issue: 1; ISSN: 2643-2609

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Abstract

Six-monthly ultrasound, with or without alpha-fetoprotein, is the surveillance strategy recommended worldwide for patients at risk of hepatocellular carcinoma. Its purpose is to find tumours while they are still curable. Pooled across the literature, ultrasound alone finds fewer than half of them at that stage.

Objectives: To review the published evidence on ultrasound and serum biomarker surveillance for hepatocellular carcinoma, with particular reference to chronic hepatitis B: what ultrasound detects and at what stage, what alpha-fetoprotein adds, how multi-marker panels compare, and what determines whether a surveillance ultrasound is interpretable at all.

Material and Methods: Narrative review of diagnostic accuracy meta-analyses, biomarker validation cohorts, imaging quality studies and society guidance indexed in PubMed and the major hepatology journals. Studies were eligible if they reported the accuracy of surveillance imaging or serum markers for hepatocellular carcinoma in a defined at-risk population, or factors affecting the performance of either. No new patient data were generated; every accuracy estimate quoted is one published by the original investigators.

Results: Pooling 32 studies, ultrasound detected hepatocellular carcinoma at any stage with 84 per cent sensitivity but early-stage disease with only 47 per cent, and the area under the curve fell from 0.96 for any stage to 0.88 for early stage. Adding alpha-fetoprotein raised early-stage sensitivity from 45 to 63 per cent, a significant gain ($p = 0.002$) at a small cost in specificity. Multi-marker panels performed better: a serum score combining sex, age, alpha-fetoprotein, its L3 isoform and des-gamma-carboxy prothrombin achieved an area under the curve of 0.95 against 0.82 for ultrasound ($p < 0.01$), rising to 0.98 when combined with ultrasound. In a European cohort of patients with chronic hepatitis B, the same score reached 0.96, and 0.94 for early-stage disease against 0.86 for alpha-fetoprotein alone.

Conclusion: The evidence does not support ultrasound alone as an adequate surveillance test. Alpha-fetoprotein should be added, and serum panels outperform both in reported cohorts, though they have been validated largely in populations with high disease prevalence and prospective surveillance data remain limited. Ultrasound quality is a further modifiable determinant that is rarely reported.

Abbreviations: HCC – Hepatocellular Carcinoma, HBV – Hepatitis B Virus, CHB – Chronic Hepatitis B, AFP – Alpha-Fetoprotein, AFP-L3 – Lens Culinaris Agglutinin-Reactive AFP, DCP – Des-Gamma-Carboxy Prothrombin, GALAD – Gender, Age, AFP-L3, AFP and DCP model, US – Ultrasound, MRI – Magnetic Resonance Imaging, AUC – Area Under the Receiver Operating Characteristic Curve, BCLC – Barcelona Clinic Liver Cancer, NPV – Negative Predictive Value.

Keywords: Hepatocellular Carcinoma; Chronic Hepatitis B; Surveillance; Alpha-Fetoprotein; GALAD Score

Introduction

Liver cancer remains among the leading causes of cancer death worldwide, and its incidence has been rising in settings where other cancers are falling [1,2]. Chronic hepatitis B infection is the dominant cause globally, and unlike most risk factors for hepatocellular carcinoma it confers risk even in the absence of cirrhosis, which widens the population for whom surveillance is recommended [3].

The rationale for surveillance is that outcome depends almost entirely on stage at detection. Curative treatment is available for early tumours and not for advanced ones, so a test that finds disease late has little value however accurate it is overall [3,4]. Society guidance therefore recommends six-monthly abdominal ultrasound, with alpha-fetoprotein recommended alongside it in some guidelines and treated as optional in others [3,4,5].

That divergence between guidelines is itself informative, and it reflects a genuine uncertainty about how much alpha-fetoprotein adds and at what cost in false positives [6,7]. Meanwhile the reference test, ultrasound, is operator-dependent and its performance in an individual patient depends on body habitus and liver morphology in ways that are not usually recorded [8,9,10].

The aim of this review is to set out what the pooled evidence shows ultrasound achieves, what alpha-fetoprotein and multi-marker panels add, and how these findings apply to the hepatitis B population specifically.

Material and Methods

Search strategy: PubMed and the archives of the major hepatology and oncology journals were searched for studies of hepatocellular carcinoma surveillance. Search terms combined hepatocellular carcinoma with surveillance, screening, ultrasound, alpha-fetoprotein, AFP-L3, des-gamma-carboxy prothrombin, GALAD, chronic hepatitis B, early detection and image quality. Reference lists of retrieved meta-analyses and guidelines were screened by hand.

Eligibility: Studies were included if they reported the accuracy of surveillance imaging or serum biomarkers for hepatocellular carcinoma in a defined at-risk population; factors affecting the performance of either; or society guidance defining current surveillance practice. Studies in mixed-aetiology cirrhosis cohorts are included where they provide the best available pooled estimates and are identified as such.

Data extraction and handling: Design, sample size, comparator, stage definition and reported accuracy estimates with confidence intervals were extracted as published. Sensitivity is reported separately for any-stage and early-stage disease throughout, because the two differ substantially and only the second is clinically meaningful for surveillance. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

Ultrasound finds tumours, but often too late: The definitive synthesis pooled 32 studies of surveillance imaging in patients with cirrhosis. Ultrasound detected hepatocellular carcinoma at any stage with 84 per cent sensitivity (95% CI 76-92), but detected early-stage disease with only 47 per cent sensitivity (95% CI 33-61) (Figure 1) [6]. In the subset of studies reporting both measures, the area under the curve was 0.96 (95% CI 0.94-0.98) for any stage and significantly lower at 0.88 (95% CI 0.85-0.90) for early detection (Figure 2) [6].

That gap is the central problem. A test used to find curable disease that identifies fewer than half of curable tumours is performing at close to the level of chance for the purpose it is deployed for, even though its headline sensitivity looks respectable. Independent Cochrane assessment and earlier health technology evaluation reached compatible conclusions [7,11].

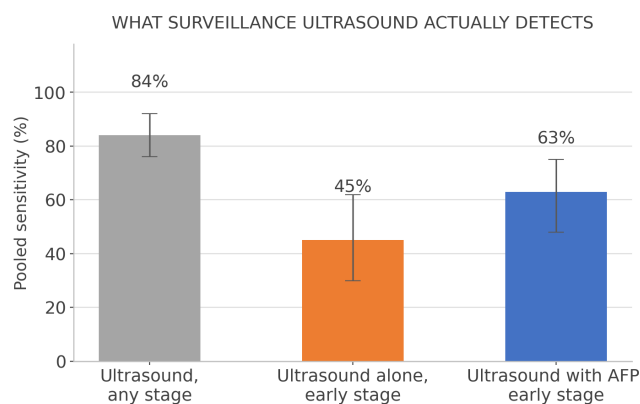


Figure 1: Pooled sensitivity of surveillance ultrasound, with and without alpha-fetoprotein, by stage at detection [6]

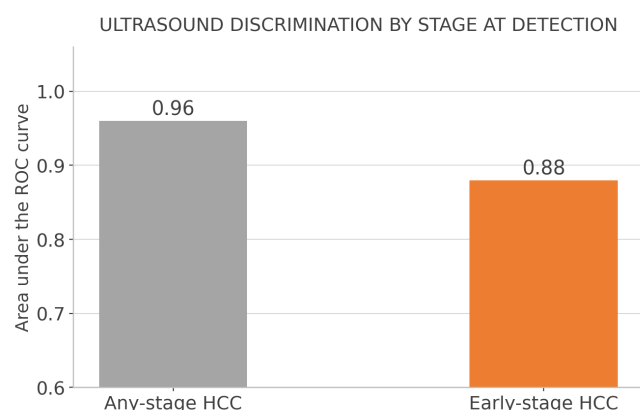


Figure 2: Area under the curve for ultrasound at any stage against early stage, from the same pooled analysis [6]

What alpha-fetoprotein adds: In studies directly comparing ultrasound with and without the marker, early-stage sensitivity rose from 45 per cent (95% CI 30-62) to 63 per cent (95% CI 48-75), a significant improvement ($p = 0.002$), at a small but statistically significant cost in specificity [6]. The investigators concluded that ultrasound with alpha-fetoprotein should be the preferred strategy until better tools exist [6].

The marker has known weaknesses that explain why it was ever considered optional. Its accuracy varies with the degree of hepatic inflammation, performing better when transaminases are normal [12], and several patient and disease factors alter its performance in cirrhosis [13]. It is nonetheless cheap, universally available and additive, which is the practical case for including it [3,6].

Multi-marker panels outperform both: The alternative to a single marker is a model. A score combining sex, age, alpha-fetoprotein, its L3 isoform and des-gamma-carboxy prothrombin was compared directly with ultrasound in a single-centre cohort of 111 patients with hepatocellular carcinoma and 180 controls with cirrhosis or chronic hepatitis B, and in a multicentre cohort of 233 early cases and 412 controls. The score achieved an area under the curve of 0.95 (95% CI 0.93-0.97) against 0.82 for ultrasound ($p < 0.01$), with sensitivity of 91 per cent and specificity of 85 per cent at the optimal cutoff (Figure 3) [14].

Performance held up for early-stage disease at 0.92 (95% CI 0.88-0.96), and combining the score with ultrasound raised the area under the curve further to 0.98 (95% CI 0.96-0.99), with sensitivity of 95 per cent [14]. The component markers each contribute: des-gamma-carboxy prothrombin has independent diagnostic value [15,16] and the L3 isoform adds specificity over total alpha-fetoprotein [17].

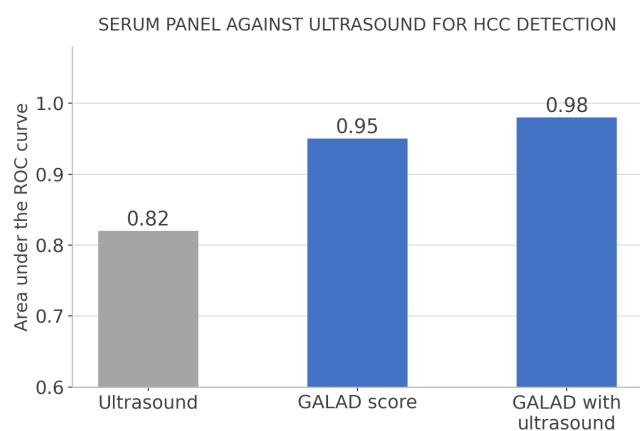


Figure 3: Serum biomarker score against ultrasound, and the two combined, for hepatocellular carcinoma detection [14]

Study	n	Design	Principal reported finding
Thompson Coon et al. 2007 [11]	—	HTA review	Surveillance evaluated systematically and economically
Gopal et al. 2014 [13]	—	Cohort	Factors affecting AFP accuracy in cirrhosis
Simmons et al. 2017 [8]	—	Cohort	Predictors of adequate ultrasound quality
Tzartzeva et al. 2018 [6]	32 studies	Meta-analysis	Early-stage sensitivity 47%; AFP raises it to 63%
Yang et al. 2019 [14]	936	Two cohorts	Serum score AUC 0.95 against 0.82 for ultrasound
Schotten et al. 2021 [18]	573	Cohort	Score AUC 0.96 in the hepatitis B population
Chong et al. 2022 [10]	—	Cohort	Ultrasound quality associated with test performance

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

Performance in hepatitis B specifically: Most surveillance evidence comes from mixed-aetiology cirrhosis cohorts, so aetiology-specific data matter. In a European study enrolling 182 patients with hepatitis B, 223 with hepatitis C and 168 with other causes of chronic liver disease, the same serum score achieved an area under the curve of 0.96 in the hepatitis B population. Restricted to very early and early stage disease across the whole cohort, the score reached 0.94, against 0.86 for alpha-fetoprotein alone, 0.83 for its L3 isoform and 0.83 for des-gamma-carboxy prothrombin (Figure 4) [18].

Two features of hepatitis B make this relevant beyond the numbers. Risk persists without cirrhosis, so a substantial share of the surveillance population has a structurally normal liver in which ultrasound is easier to interpret but the pretest probability is lower. And the population is large, so the absolute number of false positives generated by any marker threshold is correspondingly large [3,5].

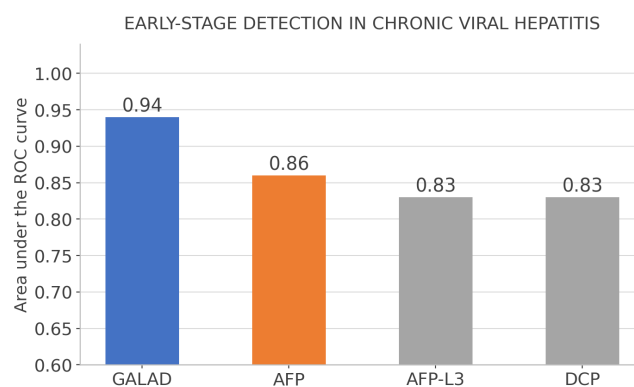


Figure 4: Early-stage detection by the combined score against its individual component markers in chronic viral hepatitis [18]

The quality of the ultrasound is a modifiable variable: A surveillance ultrasound that cannot visualise the liver adequately provides no information, and this is common enough to matter. Predictors of inadequate quality have been characterised [8], quality varies within the same patient over time [9], and image quality is directly associated with test performance for surveillance [10]. Echo pattern of the underlying liver also affects detection [19], as do broader factors influencing surveillance efficacy in cirrhosis [20].

This is arguably the most tractable finding in the field. Unlike the sensitivity of the modality itself, which is fixed, the proportion of studies that are technically adequate can be improved by protocol, by operator training and by recording a visualisation score so that inadequate studies trigger alternative imaging rather than false reassurance [8,9,10].

Strategy	Early-stage sensitivity	Principal limitation
Ultrasound alone	45-47% [6]	Misses more than half of curable tumours; operator dependent [6,8]
Ultrasound with AFP	63% [6]	Small loss of specificity; AFP varies with inflammation [6,12]
Serum multi-marker score	AUC 0.92-0.94 [14,18]	Validated in high-prevalence cohorts; limited prospective data [14,18]
Score with ultrasound	AUC 0.98 [14]	Single-centre derivation; requires both tests [14]

Table 2: Surveillance strategies with reported performance and the limitation described for each

Discussion

The uncomfortable conclusion is that the recommended test performs poorly at the task it is recommended for. Ultrasound detects 84 per cent of hepatocellular carcinomas but only 47 per cent while they remain early-stage [6], and the second figure is the one that determines whether surveillance changes outcome. Reporting the first without the second, as is common, overstates what the strategy achieves.

Adding alpha-fetoprotein is the intervention with the best evidence and the lowest cost, raising early-stage sensitivity by roughly eighteen percentage points for a small specificity penalty [6]. Guidelines that treat it as optional are difficult to defend on the pooled data, and the current major guidance now recommends it alongside ultrasound [3].

Why the panel results should be read cautiously

Multi-marker scores report areas under the curve above 0.9 and outperform ultrasound in head-to-head comparison [14,18], which is

a genuinely promising result. But those figures come from case-control designs in which cases already have diagnosed cancer and controls have chronic liver disease, and the model was developed and validated in cohorts with hepatocellular carcinoma prevalence between roughly a third and a half. Surveillance populations have prevalence measured in low single-digit percentages per year, and positive predictive value falls steeply as prevalence falls.

The same caution applies to the combined score plus ultrasound result of 0.98, which was obtained in the single-centre derivation cohort [14]. Until a panel is tested prospectively in an unselected surveillance population with clinical endpoints, the reported discrimination should be treated as an upper bound.

Study limitations

The limitations belong to the underlying literature. The pooled imaging estimates derive predominantly from cirrhosis cohorts of mixed aetiology, so their applicability to non-cirrhotic hepatitis B is inferred rather than demonstrated [6,7]. Biomarker cohorts are case-control in design and enriched for disease [14,18]. Assay platforms for the L3 isoform and des-gamma-carboxy prothrombin differ between laboratories and are not universally available, which limits transferability of published cutoffs [15,16,17]. Ultrasound quality is inconsistently reported across studies, so the pooled sensitivity figures conflate technically adequate and inadequate examinations [8,9,10]. Few studies report surveillance harms alongside benefits, and none reviewed here quantifies the downstream investigation burden generated by false positives.

Two gaps deserve naming. No randomised comparison has tested a biomarker-panel surveillance strategy against ultrasound with alpha-fetoprotein with mortality as the endpoint. And no study reviewed here reports surveillance performance stratified by whether the patient with hepatitis B has cirrhosis, which is the distinction that most affects both pretest probability and image interpretability [3,5].

Conclusion

Surveillance ultrasound detects most hepatocellular carcinomas eventually and fewer than half while they are still early. Alpha-fetoprotein adds about eighteen percentage points of early-stage sensitivity for a modest specificity cost and should be used alongside it rather than treated as optional. Multi-marker serum scores outperform both in reported cohorts, including specifically in chronic hepatitis B, but were developed in populations with far higher disease prevalence than any surveillance programme and have not been tested prospectively against clinical endpoints. In the meantime the most tractable improvement is not a new marker but recording whether the ultrasound was technically adequate, because an uninterpretable study currently returns the same reassuring report as a normal one.

Acknowledgements

The pooled analyses and validation cohorts behind this article were assembled by other groups, and we are indebted to them for the work.

Funding

Preparation of this article drew on no external grant, sponsorship or institutional funding whatsoever.

Conflict of Interest

Not one of the authors has a competing interest to report.

Ethics Statement

Only material that is already published has been examined here. Nobody was recruited and no new clinical records were opened, so ethics approval was not needed.

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Citation: Zhang W, Farouk O, Meyer C. "Ultrasound and Biomarker-Based Surveillance for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection: A Review." *Ann Gastroenterol Dig Disord* (2025) Volume 8, Issue 1 doi: 10.5281/zenodo.22202911