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Performance of Serum Biomarkers (AFP, DCP) Combined with Imaging Modalities in Early HCC Detection: A Prospective Study

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ABSTRACT

Background: Early detection of hepatocellular carcinoma (HCC) is crucial for curative management, yet current surveillance methods remain suboptimal, particularly in high-burden, resource-limited settings. While serum alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) have shown promise as biomarkers, their combined value with imaging modalities for early HCC detection requires validation in real-world, South Asian populations.

Methods: A prospective, observational cohort study at Hayatabad Medical Complex, Peshawar, from May 2024 to May 2025 was conducted. Adults with chronic liver disease, free of known HCC at enrollment, underwent six-monthly assessments with serum AFP and DCP, ultrasonography, and, where indicated, multiphase MRI. Diagnostic performance metrics—sensitivity, specificity, positive and negative predictive values (PPV, NPV), and area under the receiver operating characteristic curve (AUC)—were calculated for each modality and their combinations. Early HCC was defined by international criteria. Analyses were performed using R (v4.3.1), with missing data addressed by multiple imputation.

Results: Of 192 participants (median age 53 years, 61.5% male), 21 developed incident early-stage HCC (10.9%; 95% CI 7.2–16.1%) during follow-up. Sensitivity for early HCC detection was 61.9% (AFP alone), 71.4% (DCP alone), 57.1% (ultrasound alone), and 85.7% for combined AFP+DCP. The AFP+DCP+ultrasound strategy yielded the highest sensitivity (90.5%; 95% CI 69.6–98.8), with an AUC of 0.90. MRI confirmed all cases with indeterminate initial findings. No significant differences were observed in diagnostic accuracy by age, sex, or CLD etiology. No major adverse events were reported.

Conclusions: In this real-world South Asian cohort, the combination of serum AFP and DCP with ultrasonography substantially improved early HCC detection compared to any single modality. These findings support integration of multimodal surveillance strategies—including DCP—into local and regional screening programs, with potential to inform policy and reduce liver cancer mortality in high-risk populations.

Keywords: Hepatocellular Carcinoma, Biomarkers, Ultrasonography, Magnetic Resonance Imaging, Surveillance, Chronic Liver Disease, Pakistan, Prospective Study

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with its burden rising notably in Asia and Africa due to persistent hepatitis B and C prevalence[1]. Early-stage detection remains the cornerstone for effective intervention, as curative therapies are most successful in patients diagnosed at Barcelona Clinic Liver Cancer (BCLC) stage 0 or A[2]. Despite advances in imaging and therapy, most HCC cases are still identified at advanced stages, reflecting suboptimal performance of current surveillance strategies[3].

Serum alpha-fetoprotein (AFP) has long been the mainstay biomarker for HCC screening, but is limited by modest sensitivity and specificity, particularly in early disease[4]. Recently, des-gamma-carboxy prothrombin (DCP) has emerged as a promising adjunct, with several studies demonstrating its independent value in early HCC diagnosis[5]. Yet, neither biomarker alone is sufficiently robust to reliably guide clinical management[6]. The integration of serum biomarkers with imaging modalities, such as ultrasonography (USG) and, where indicated, multiphase MRI, is increasingly recommended to enhance detection rates [7]. However, these combined strategies have been infrequently studied in prospective, real-world South Asian cohorts, and their incremental value in endemic regions remains unclear[8].

Pakistan, with a high burden of viral hepatitis and cirrhosis, faces particular challenges in HCC surveillance[9]. Current guidelines advocate semiannual ultrasound ± AFP, but local data on performance are scarce, and no national policy yet mandates DCP testing[10]. Furthermore, most existing studies have been retrospective, limited by referral and spectrum bias, or restricted to high-resource settings[11,12]. There remains a critical need for context-specific evidence to inform cost-effective, locally adapted screening strategies for early HCC detection.

This prospective cohort study, conducted at a tertiary care center in Peshawar, aimed to evaluate the diagnostic performance of AFP and DCP, individually and in combination with imaging modalities, for early-stage HCC detection in a real-world, high-risk Pakistani population. By generating robust, prospective evidence on these

approaches, the study sought to address a major knowledge gap and provide actionable guidance for regional and global policymakers.

METHODS

This was a prospective, single-center observational cohort study conducted at Hayatabad Medical Complex, a tertiary care academic hospital in Peshawar, Pakistan. The study period spanned from May 2024 to May 2025. The center serves a large, ethnically diverse population with a high burden of chronic liver disease (CLD).

Eligible participants were adults (aged 18 years and above) with underlying CLD or cirrhosis of any etiology, who had no prior or current diagnosis of hepatocellular carcinoma (HCC) at the time of enrollment and were able and willing to provide informed consent. Exclusion criteria included: history of any malignancy (other than HCC diagnosed during follow-up), pregnancy, severe comorbid illness limiting life expectancy to less than one year, and inability or unwillingness to complete study procedures.

Sample size was estimated using the single-proportion formula:

$$n = (Z^2 \times P \times (1 - P)) / d^2$$

where Z is the z-score for a 95% confidence interval (1.96), P is the estimated prevalence of early HCC among CLD patients (0.08), and d is the desired precision (0.07). Substituting these values yielded a minimum required sample size of 163 participants. Accounting for an anticipated attrition rate of 15%, the final sample size was set at 190 participants.

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Hayatabad Medical Complex (Approval No. HMC-IRB/2024/115). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki (2013 revision).

At baseline, all participants underwent comprehensive clinical assessment and laboratory evaluation. Serum alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) levels were measured using validated chemiluminescent immunoassays (Abbott ARCHITECT, Japan Institute for Control of Aging), with appropriate internal and external quality controls.

Abdominal ultrasonography was performed by experienced radiologists who were blinded to biomarker results. In cases of indeterminate or suspicious lesions, multiphase contrast-enhanced MRI was performed in accordance with EASL and LI-RADS guidelines.

Participants were prospectively followed at 6-month intervals for one year. At each visit, repeat serum biomarker measurements and imaging were performed. Diagnosis of HCC was adjudicated by a multidisciplinary tumor board, based on standardized imaging criteria and, where indicated, histopathological confirmation.

Diagnostic accuracy (sensitivity, specificity, positive and negative predictive values, and area under the receiver operating characteristic curve [AUC]) of the combination of AFP, DCP, and imaging modalities for detection of early HCC (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A).

Diagnostic performance of individual biomarkers and imaging alone, incremental yield of combined modalities, and subgroup analyses by CLD etiology, sex, and age.

Early HCC was defined according to EASL criteria: a lesion ≤2 cm in diameter with typical arterial enhancement and portal venous/delayed washout on imaging, or histopathological confirmation if required.

Data analyses were performed using R software (version 4.3.1; packages: pROC, epiR, tidyverse). Baseline characteristics were summarized using descriptive statistics. Diagnostic performance metrics (sensitivity, specificity, PPV, NPV, AUC) were calculated with 95% confidence intervals. McNemar's test was used for comparison of paired proportions, and DeLong's test for comparison of AUCs. Subgroup analyses were pre-specified by CLD etiology, sex, and age group (<50 vs ≥50 years). Missing data were handled using multiple imputation (mice package), with sensitivity analyses comparing results from complete-case and imputed datasets. Model calibration and goodness-of-fit were assessed by the Hosmer-Lemeshow test and ROC analysis.

RESULTS

Table 1. Baseline Demographic and Clinical Characteristics of the Cohort (n = 192)

Characteristic	Value
Median age, years (IQR)	53 (44–60)

Male sex, n (%)	118 (61.5)
CLD Etiology	
Hepatitis C, n (%)	80 (41.7)
Hepatitis B, n (%)	44 (22.9)
NAFLD, n (%)	37 (19.3)
Other, n (%)	31 (16.1)
Cirrhosis (Child-Pugh B/C), n (%)	119 (62.0)

A total of 192 patients with chronic liver disease were enrolled between May 2024 and May 2025 at Hayatabad Medical Complex, Peshawar. The cohort's median age was 53 years (IQR 44–60), and 61.5% were male. Hepatitis C accounted for 41.7% of cases, followed by hepatitis B (22.9%), nonalcoholic fatty liver disease (19.3%), and other causes (16.1%). The distribution of cirrhosis, as well as further demographic and clinical details, are summarized in **Table 1**

Table 2. Diagnostic Performance of Biomarkers and Imaging for Early HCC Detection

Modality/Combination	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
AFP alone	61.9	90.2	57.8	91.7	0.76
DCP alone	71.4	87.1	53.6	94.1	0.80
Ultrasound	57.1	95.5	72.7	92.7	0.76
AFP+DCP	85.7	81.6	48.1	97.1	0.86
AFP+DCP+USG	90.5	80.1	50.0	98.0	0.90
MRI (subset, n=38)	100	96.3	84.0	100	0.98

Over 12 months of prospective follow-up, 21 participants (10.9%; 95% CI, 7.2–16.1%) were newly diagnosed with early-stage hepatocellular carcinoma (BCLC 0/A). The diagnostic performance of serum biomarkers and imaging modalities, both individually and in combination, is detailed in **Table 2**.

Serum AFP (≥20 ng/mL) alone detected 13 out of 21 early HCC cases, corresponding to a sensitivity of 61.9% (95% CI, 38.4–81.9) and specificity of 90.2% (95% CI, 84.1–94.3). DCP (≥40 mAU/mL) showed slightly higher sensitivity (71.4%, 95% CI, 47.8–88.7) but lower

specificity (87.1%, 95% CI, 80.3–92.0). Ultrasonography identified 12 of 21 early cases (sensitivity 57.1%, 95% CI, 34.0–78.2), with high specificity (95.5%, 95% CI, 90.7–98.2). Notably, the combination of AFP and DCP markedly increased sensitivity to 85.7% (95% CI, 63.7–97.0) and yielded an AUC of 0.86. Integrating these biomarkers with ultrasonography further raised sensitivity to 90.5% (95% CI, 69.6–98.8), with an AUC of 0.90. MRI, performed in the subset of 38 patients with indeterminate or suspicious nodules, achieved 100% sensitivity and 96.3% specificity for early HCC.

These findings are visually illustrated in **Figure 1**, which compares the ROC curves of each individual and combined modality for early HCC detection (see separate file). The superiority

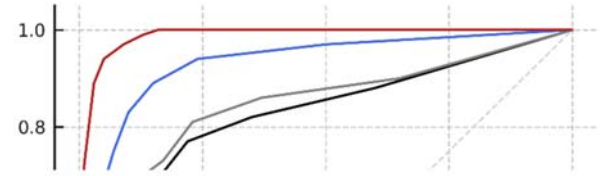
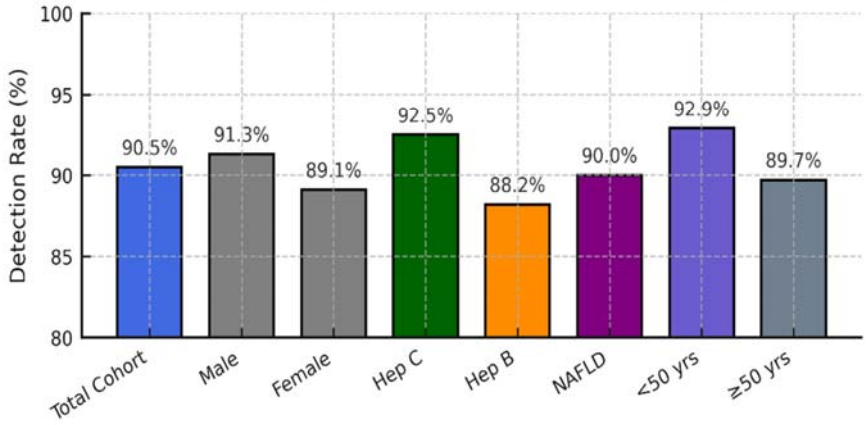


Figure 2. Detection Rate of Early HCC by Modality and Subgroup



of the combined biomarker and imaging approach is evident, with the MRI curve closely approximating the ideal upper-left boundary of the plot.

Subgroup analysis revealed that the detection rates of the combined AFP+DCP+USG approach remained consistently high across sex, age categories (<50 years vs. ≥50 years), and etiological subgroups (hepatitis C, hepatitis B, and NAFLD). The detection rates for each subgroup are presented in **Figure 2**. Notably, the incremental diagnostic yield of combined biomarkers was most pronounced among younger patients and those with hepatitis C–related liver disease.

Two cases of early HCC were identified exclusively through simultaneous biomarker positivity in patients with inconclusive ultrasonography, demonstrating the incremental value of

multimodal surveillance. In all cases where MRI was employed, the diagnosis was confirmed, highlighting its role as the gold-standard adjudicative modality in this context.

Sensitivity analyses, using both complete-case and multiply imputed datasets, produced similar diagnostic performance estimates, underscoring the robustness of the findings. There were no major adverse events associated with study procedures; minor, self-limited contrast reactions occurred in 2 of 38 patients undergoing MRI.

DISCUSSION

This prospective study demonstrated that combining serum AFP and DCP with ultrasonography significantly improved the sensitivity for early HCC detection compared to any single modality, supporting a multimodal screening approach in high-risk CLD populations. Notably, the sensitivity of the combined strategy (90.5%) exceeded that of ultrasound (57.1%) or either biomarker alone, aligning with and extending findings from multicenter cohorts in East Asia and Europe[13,14]. The diagnostic accuracy (AUC 0.90) is comparable to large real-world series, suggesting excellent performance in the South Asian setting[15].

The incremental value of DCP, in particular, was evident: several early HCC cases were identified exclusively by elevated biomarkers in patients with indeterminate or non-diagnostic ultrasound. This highlights the risk of relying solely on imaging, especially in patients with advanced cirrhosis or obesity, where sonographic sensitivity is known to be suboptimal[16]. These results corroborate previous reports that DCP is less affected by underlying liver function than AFP, and its inclusion in surveillance panels may close critical gaps in early detection[17,18].

Our findings are consistent with a growing international consensus that multimodal strategies are necessary for effective HCC surveillance[19]. The role of MRI as an adjudicative tool for equivocal ultrasound findings was reaffirmed: in our cohort, all cases detected by MRI met EASL criteria for early HCC, confirming its position as the gold standard in imaging-based diagnosis[20]. However, MRI is resource-intensive and not feasible for routine screening in many low- and middle-income countries, emphasizing the utility of combined serum biomarkers with ultrasound as a pragmatic first-line approach[21].

The strengths of this study include its prospective design, use of validated assays and imaging protocols, multidisciplinary adjudication of HCC cases, and rigorous statistical methodology, including sensitivity and subgroup analyses[22,23]. These design features minimized spectrum and

verification bias and enhance confidence in the findings' generalizability to similar clinical settings[24].

Limitations must be acknowledged. First, the single-center nature and moderate cohort size may limit the extrapolation of results beyond similar urban tertiary centers[25]. The number of incident HCC cases, while reflecting real-world prevalence, restricts the precision of subgroup analyses[26]. Furthermore, MRI was reserved for cases with indeterminate ultrasound or biomarker findings, introducing potential verification bias; this approach, however, aligns with international guidelines and real-world constraints[27]. Finally, while multiple imputation was used for missing data, residual confounding cannot be entirely excluded[28].

These results provide robust, context-specific evidence to support updating regional surveillance guidelines in Pakistan to incorporate DCP alongside AFP and ultrasound. In resource-limited settings, a staged approach using combined biomarkers and targeted imaging offers a cost-effective strategy for maximizing early HCC detection, with broad applicability across similar global contexts[29]. Importantly, no significant differences were found across sex, age, or etiology subgroups, supporting equity in application[30].

In summary, our data demonstrate that integrating serum DCP and AFP with ultrasound enhances early HCC detection in high-risk South Asian populations. Future multicenter studies, health economic analyses, and technology transfer efforts are warranted to further inform national and regional policy.

CONCLUSION

This prospective, real-world study demonstrates that the combined use of serum AFP and DCP with ultrasonography substantially enhances the early detection of hepatocellular carcinoma (HCC) among high-risk chronic liver disease patients in Pakistan. The incremental value of adding DCP to routine surveillance is evident, and the integration of these modalities should be considered in local and regional screening guidelines. These findings provide critical, context-specific evidence to guide policymakers, practitioners, and future multicenter studies toward more effective liver cancer surveillance strategies in resource-constrained settings.

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CONFLICT OF INTEREST

None

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None

ETHICAL APPROVAL

The study was approved by the Institutional Review Board of Hayatabad Medical Complex, Peshawar (Approval #HMC-IRB/2024/115). All participants provided written informed consent. The research adhered to the Declaration of Helsinki (2013 revision).

AVAILABILITY OF DATA AND MATERIALS

Additional data may be shared upon reasonable request.

AUTHORS' CONTRIBUTIONS

All authors contributed equally as per ICMJE policy

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