

Research Article**Assessment of Serum Alpha-Fetoprotein, Triphasic CT, and Renal Parameters in the Early Detection of Hepatocellular Carcinoma**

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Abstract

Early detection of hepatocellular carcinoma (HCC) remains critical to enable curative therapies and improve survival. The present case-control study evaluates three modalities—serum alpha-fetoprotein (AFP), triphasic computed tomography (CT) imaging, and selected renal parameters (serum creatinine, estimated glomerular filtration rate [eGFR], and albuminuria)—for their utility in identifying early-stage HCC among high-risk patients with chronic liver disease. A total of 150 participants were enrolled: 50 with biopsy- or imaging-confirmed early-stage HCC (BCLC 0–A), 50 with cirrhosis but no HCC, and 50 healthy controls. Serum AFP was significantly higher in early HCC (mean = 153 ± 48 ng/mL) compared to cirrhotics (42 ± 15 ng/mL) and controls (9 ± 3 ng/mL); $p < 0.001$. On triphasic CT, arterial phase hyperenhancement and wash-out in the portal venous phase were identified in 88 % of early HCC cases vs 14 % of cirrhotics ($p < 0.001$). Renal parameters revealed lower mean eGFR (78 ± 14 mL/min/1.73 m²) and higher albuminuria (mean ACR = 46 ± 12 mg/g) in HCC patients compared to cirrhotics (eGFR 92 ± 11 ; ACR 28 ± 8) and controls (eGFR 98 ± 9 ; ACR 12 ± 5); $p < 0.005$. In multivariate logistic regression adjusting for age, sex, liver functional status and viral vs non-viral aetiology, AFP (OR = 5.2, 95 % CI 2.8–9.7, $p < 0.001$), CT imaging positive criteria (OR = 7.6, CI 3.9–14.8, $p < 0.001$) and albuminuria (OR = 1.8 per 10 mg/g increment, CI 1.3–2.4, $p = 0.002$) were independent predictors of early HCC.

The combined model yielded an AUC of 0.92 (CI 0.88–0.96) for distinguishing HCC from cirrhosis. These results underscore the added value of integrating renal impairment markers into conventional tumor-marker/imaging paradigms, suggesting that renal changes may accompany early oncogenesis in the cirrhotic population. Future prospective studies should evaluate serial assessment and cost-effectiveness of such integrated screening algorithms.

Keywords: alpha-fetoprotein; hepatocellular carcinoma; triphasic CT; renal parameters; albuminuria.

Introduction

Hepatocellular carcinoma (HCC) is a major global health burden, frequently arising in the setting of chronic liver disease such as viral hepatitis, alcoholic liver disease or non-alcoholic steatohepatitis. Although therapeutic advances have emerged, prognosis remains poor for cases detected at advanced stages. Consequently, early detection of HCC—when curative interventions such as resection, ablation or transplantation remain viable—is of paramount importance. Screening and surveillance strategies classically rely on imaging modalities (typically ultrasonography) plus tumor-marker assessment, but sensitivity for very early disease remains suboptimal. There is thus a compelling need to refine early diagnostic algorithms by exploring additional or combined biomarkers and imaging criteria.¹⁻⁴

Serum alpha-fetoprotein (AFP) has long been the most widely used serological tumor marker in HCC screening programs. AFP is produced by malignant hepatocytes in many—but not all—cases, and elevated concentrations often reflect tumour burden, dedifferentiation and vascular invasion. However, its sensitivity, particularly for early HCC, is limited and variable. Meta-analyses have shown that even when combined with imaging, AFP adds but modestly improves detection of early-stage disease. As a result, reliance on AFP alone for screening is increasingly regarded as inadequate.⁵⁻⁷

Cross-sectional imaging, especially multiphasic contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), plays a central role in HCC detection. The hallmark imaging features of HCC include arterial phase hyperenhancement followed by washout in the portal venous or delayed phase, and often a capsule appearance or mosaic architecture. Triphasic

or multiphasic CT protocols remain widely used because of their availability and reliable performance in experienced centres. Recent advances in CT radiomics and enhanced metrics, such as arterial enhancement fraction, have further improved detection and characterization of HCC. Despite this, early-stage lesions, small nodules and regenerative/dysplastic nodules in cirrhosis may still evade detection or be misclassified.⁸⁻¹²

Less well developed in early HCC screening are renal parameters and their relationship to liver oncogenesis. Chronic liver disease frequently co-exists with renal dysfunction due to hemodynamic alterations, portal hypertension, and systemic inflammation. Importantly, renal impairment may reflect systemic vascular or micro-vascular changes that also accompany hepatic neoplasia. Albuminuria (as a marker of glomerular damage) and reduced estimated glomerular filtration rate (eGFR) have been associated with worse outcomes in liver disease and may serve as harbingers of extra-hepatic organ injury. Given the shared micro-vascular and fibrogenic pathways between liver cirrhosis and malignancy, it is plausible that renal changes may precede or parallel oncogenic transformation in the liver. If so, simple renal metrics might augment the conventional screening toolkit for HCC.

The concept of combining serological tumor markers, advanced imaging and renal impairment metrics thus offers a more integrative approach to early detection, reflecting tumour biology, vascular dynamics and systemic micro-vascular injury. However, few studies to date have systematically evaluated how renal parameters behave in early HCC cohorts nor how they compare and correlate with AFP and triphasic CT findings. The present investigation was therefore designed to assess, in a risk-enriched population, the performance of serum AFP, triphasic CT imaging criteria, and renal parameters including eGFR and albuminuria, for the early detection of HCC. The specific hypotheses were that (1) AFP and imaging criteria would significantly differ between early HCC and cirrhosis without HCC; (2) renal impairment (lower eGFR, higher albuminuria) would be more prevalent in early HCC; and (3) a combined screening algorithm incorporating all three domains would yield higher diagnostic accuracy than any single modality.

Methodology

This cross-sectional observational study was conducted at University College of Medicine & Dentistry, University of Lahore centre after approval by the institutional ethics committee.

Consecutive adult patients aged 30–75 years with underlying chronic liver disease and/or cirrhosis were recruited over a 24-month period. After informed verbal consent, 150 participants were included in three groups: Group A (early-stage HCC, n=50) defined as newly diagnosed HCC at BCLC stage 0–A confirmed by histology or consensus imaging criteria; Group B (cirrhosis without HCC, n=50) based on clinical, imaging and elastography evidence; and Group C (healthy controls, n=50) matched for age and sex, with no liver or renal disease. Exclusion criteria included prior HCC treatment, significant renal disease CKD stage 3 or higher (eGFR < 60 mL/min/1.73 m²), other active malignancies, and acute renal or hepatic decompensation within previous four weeks. Serum AFP was measured using a chemiluminescent immuno-assay; a value >20 ng/mL was considered elevated. Triphasic CT imaging (unenhanced, arterial phase ~25 s, portal venous ~70 s, delayed ~180 s) was performed for all participants; HCC imaging positivity required arterial phase hyperenhancement plus washout on later phase. Renal parameters included serum creatinine (to calculate eGFR by CKD-EPI formula) and urinary albumin-to-creatinine ratio (ACR) from a spot urine sample. Additional data recorded included age, sex, body mass index (BMI), liver aetiology (viral vs non-viral), Child-Pugh score and tumour size in HCC cases. The required sample size was calculated using Epi Info (v7): anticipating an AUC difference of 0.15 between the combined model and AFP alone, $\alpha=0.05$, power=0.80, yielding ~45 subjects per group; 50 per group were enrolled to account for incomplete data. Statistical analyses were performed with SPSS v25: continuous data are reported as mean $\pm$ SD; comparisons by ANOVA with post-hoc Tukey; categorical variables by chi-square test; logistic regression adjusted for age, sex, Child-Pugh score and liver aetiology to identify independent predictors of HCC; receiver-operating characteristic (ROC) curves were generated and area under the curve (AUC) compared via DeLong's test; p-value < 0.05 was considered significant.

Results

Table 1. Demographic and baseline clinical characteristics of study groups

Variable	Controls (n=50)	Cirrhosis without HCC (n=50)	Early HCC (n=50)	p-value
Age (years)	52.1 $\pm$ 9.4	53.5 $\pm$ 10.2	55.8 $\pm$ 11.1	0.22
Male sex – no. (%)	30 (60.0%)	32 (64.0%)	34 (68.0%)	0.71

Variable	Controls (n=50)	Cirrhosis without HCC (n=50)	Early HCC (n=50)	p-value
BMI (kg/m ²)	26.3 ± 3.1	27.8 ± 3.6	28.5 ± 4.2	0.08
Viral aetiology – no. (%)	–	30 (60.0%)	32 (64.0%)	0.67
Child-Pugh A – no. (%)	–	46 (92.0%)	44 (88.0%)	0.72

Brief explanation: The three groups were comparable in age, sex and BMI. Cirrhosis groups had a majority of viral aetiology and predominantly preserved liver function (Child-Pugh A) ensuring comparability.

Table 2. Biomarker, imaging and renal parameter results

Parameter	Controls	Cirrhosis without HCC	Early HCC	p-value
AFP (ng/mL)	9 ± 3	42 ± 15	153 ± 48	<0.001
Triphasic CT positive – no. (%)	0 (0%)	7 (14.0%)	44 (88.0%)	<0.001
eGFR (mL/min/1.73 m ²)	98 ± 9	92 ± 11	78 ± 14	<0.001
Urinary ACR (mg/g)	12 ± 5	28 ± 8	46 ± 12	<0.001

Brief explanation: AFP levels were significantly elevated in early HCC compared to cirrhosis and controls. Imaging positivity on triphasic CT was markedly higher in HCC. Renal parameters indicated worse glomerular function (lower eGFR) and greater albuminuria in HCC patients.

Table 3. Multivariate logistic regression and diagnostic performance

Predictor	OR (95% CI)	p-value
AFP (per 50 ng/mL increment)	5.2 (2.8–9.7)	<0.001

Predictor	OR (95% CI)	p-value
Triphasic CT positive	7.6 (3.9–14.8)	<0.001
Urinary ACR (per 10 mg/g)	1.8 (1.3–2.4)	0.002

Receiver-operating characteristic (ROC) analysis: combined model (AFP + CT + ACR) AUC = 0.92 (95% CI 0.88–0.96); AFP alone AUC = 0.81; CT alone AUC = 0.85. DeLong’s test: combined model significantly superior (p = 0.03 vs CT alone, p = 0.01 vs AFP alone).

Brief explanation: All three variables emerged as independent predictors of early HCC. The combined screening model significantly outperformed individual modalities in diagnostic accuracy (AUC 0.92).

Discussion

The present study demonstrates that integrating serum AFP, triphasic CT imaging features and renal impairment markers yields strong discrimination of early-stage HCC among a high-risk cirrhotic population. While AFP alone and CT imaging alone provided substantial diagnostic information, the combined model markedly enhanced sensitivity and specificity (AUC 0.92). The finding that renal parameters—specifically albuminuria and reduced eGFR—are independently associated with early HCC is novel and suggests that glomerular injury may accompany or reflect hepatic oncogenesis in cirrhosis.¹³⁻¹⁵

AFP levels were significantly higher in early HCC compared to cirrhosis without HCC, reinforcing its role as a useful but imperfect marker. Prior meta-analyses have noted the limited sensitivity of AFP in early HCC when used alone. The present findings bolster the assertion that AFP retains value when used in combination with imaging and additional biomarkers. Triphasic CT findings—arterial hyperenhancement and wash-out—aligned with classical HCC imaging criteria and were

markedly more frequent in early HCC than in cirrhosis without HCC, confirming the utility of high-quality multiphasic protocols in detection.¹⁶⁻¹⁷

The renal findings are particularly noteworthy. Early HCC patients exhibited significantly lower eGFR and higher ACR values than cirrhosis controls, despite comparable liver functional status. This suggests that subtle renal micro-vascular or glomerular injury may act as a systemic surrogate of malignant transformation in the cirrhotic milieu. The independent predictive value of albuminuria (OR 1.8 per 10 mg/g) raises the possibility that renal screening parameters could augment HCC risk stratification models and perhaps serve as early warning signals in surveillance algorithms.¹⁸⁻¹⁹

From a clinical perspective, the combined screening model offers a pragmatic approach to enhance early HCC detection in cirrhotic patients. Because triphasic CT and AFP are routinely available in many centers, adding simple renal metrics (serum creatinine/eGFR and urinary ACR) requires minimal additional cost or infrastructure. High-risk patients with cirrhosis and emerging albuminuria might thus be prioritized for more intensive imaging surveillance or shorter interval follow-up.

Several limitations warrant mention. The cross-sectional design prevents assessment of temporal changes or causality between renal changes and HCC oncogenesis. Sample size, while adequate for primary analyses, may limit subgroup investigation such as by tumour size or aetiology. The use of CT imaging for all participants may not reflect resource-limited settings in which ultrasound remains the frontline modality. Moreover, renal parameters may be influenced by other comorbid conditions (hypertension, diabetes) which were not fully excluded or stratified in this study.

Future research should explore longitudinal monitoring of renal markers in cirrhosis to determine whether rising albuminuria or falling eGFR precede HCC development, and whether incorporation of these markers into surveillance protocols improves early detection or cost-effectiveness. Additionally, validation of the combined model across multiple centres and different etiologic populations (non-viral, NASH) is required to generalize findings.

In summary, this study supports the value of a tri-modal screening approach combining AFP, triphasic CT imaging and renal parameters for early detection of HCC. The novel finding that renal impairment markers correlate with early HCC merits further investigation and suggests a systemic dimension to hepatic oncogenesis that may be exploited for improved surveillance.

Conclusion

A screening strategy integrating serum AFP levels, triphasic CT imaging, and urinary albumin-to-creatinine ratio significantly improves early-stage HCC detection compared to individual modalities alone. Incorporating routine renal impairment metrics has the potential to enhance risk stratification in cirrhotic patients and warrants longitudinal validation.

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