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ORIGINAL ARTICLE

DIAGNOSTIC VALUE OF SERUM SOLUBLE AXL COMPARED WITH ALPHA-FETOPROTEIN IN HEPATOCELLULAR CARCINOMA: EXPERIENCE FROM A TERTIARY CENTER IN BANGLADESH

KAWSER AKTER SWEETY[1], MD. KHAIRUL ISLAM[2], SADIA SUMA[3], MONZURUL ALAM BHUIYAN[4], FAHIMA SHARMIN HOSSAIN[5], ABHIZIT PANDIT[6], TUHIN SULTANA[7]

Abstract

Background: *Hepatocellular carcinoma (HCC) is a leading cause of mortality worldwide. In Bangladesh, early detection is frequently hindered by limited laboratory facilities. Alpha-fetoprotein (AFP) is a well-accepted blood biomarker for HCC detection, but its diagnostic accuracy is suboptimal. Recently, soluble Axl (sAxl), a protein associated with tumor progression, has emerged as a promising biomarker. This study aimed to evaluate the diagnostic performance of serum sAxl in patients with HCC and to compare its accuracy with AFP among Bangladeshi patients with cirrhosis.* ***Methods:*** *A comparative cross-sectional study was conducted in the Departments of Laboratory Medicine and Hepatology at Bangladesh Medical Universityfrom March 2024 to February 2025. Sixty-four participants were enrolled: 32 with HCC and cirrhosis (Group I) and 32 with cirrhosis alone (Group II). Serum sAxl was measured using ELISA, and AFP was measured by chemiluminescent immunoassay. Data analysis was performed with SPSS v26. Diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis, and DeLong's test was used for area under the curve (AUC) comparison.* ***Results:*** *Median AFP levels were significantly higher in HCC patients (1001 ng/ml) compared to those with cirrhosis (2.8 ng/ml;* p< *0.001). Median sAxl levels were also substantially elevated in HCC (146.4 ng/ml) relative to cirrhosis (25.6 ng/ml;* p< *0.001). AFP yielded an AUC of 0.689, sensitivity 42.9%, and specificity 81.3%. In contrast, sAxl achieved an AUC of 0.794 (p = 0.018 vs AFP by DeLong's test), with 75% sensitivity and 84.4% specificity, indicating good diagnostic discrimination between HCC and cirrhosis.* ***Conclusion:*** *Serum sAxl demonstrated greater diagnostic accuracy than AFP in distinguishing HCC from cirrhosis among Bangladeshi patients. Given its non-invasive nature and strong performance, sAxl may serve as a practical biomarker for early HCC detection in resource-limited settings.*

Keywords: *Hepatocellular carcinoma, soluble Axl, alpha-fetoprotein, biomarker, ELISA.*

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1. Consultant, Ibn Sina Diagnostic and Imaging Center, Dhanmondi, Dhaka, Bangladesh.
2. Assistant Professor, Department of Medicine, Dhaka Medical College, Dhaka, Bangladesh.
3. Lecturer , Patuakhali Medical College, Dhaka, Bangladesh.
4. Assistant Professor, Department of Laboratory Medicine, Bangladesh Medical University , Dhaka, Bangladesh.
5. Indoor Medical Officer, Dhaka Medical College Hospital, Dhaka, Bangladesh.
6. Senior Consultant, Mugda Medical College Hospital, Dhaka, Bangladesh.
7. Professor, Department of Laboratory Medicine, Bangladesh Medical University, Dhaka, Bangladesh.

Correspondence: Dr. Kawser Akter Sweety, Consultant, Ibn Sina Diagnostic and Imaging Center, Dhanmondi, Dhaka, Bangladesh. Email: sweetyimc8@gmail.com

Introduction:

Hepatocellular carcinoma (HCC) ranks as the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide.[1] Due to its aggressiveness and poor prognosis, the World Health Organization projects HCC will cause over one million deaths annually by 2030.[2,3]

Major causes of HCC include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol consumption, non-alcoholic fatty liver disease (NAFLD), diabetes, obesity, aflatoxin exposure, smoking, and other environmental toxins.[4,5] Cirrhosis, regardless of cause, is the strongest predictor of HCC. Notably, HBV can cause cancer even in non-cirrhotic livers, while HCV-related HCC usually appears with advanced fibrosis.[6]

There are marked sex and geographic disparities in HCC. It is more common in males, with East Asia and sub-Saharan Africa showing the highest incidence.[7] In 2020, about 72% of all liver cancer cases occurred in Asia.[8,9]

In Bangladesh, HCC is the third most common cancer and a growing public-health concern. Nearly two-thirds of local cases are linked to chronic HBV infection. The highest reported prevalence is found in Dhaka and Chittagong.[10,11]

Early diagnosis is difficult because HCC often remains asymptomatic until advanced stages.[12] Curative treatments such as surgical resection and liver transplantation can achieve 5-year survival rates above 70%. However, these options are only viable for early-stage disease.[13] Most Bangladeshi patients present at a late stage, when limited therapies are available.[14]

Serum alpha-fetoprotein (AFP) is still the most widely used biomarker for HCC detection. Its diagnostic performance, however, varies by population and tumor stage. Sensitivity for small or early tumors often falls below 60%.[15] AFP can also rise in benign liver conditions such as chronic hepatitis or cirrhosis. This leads to false positives and diagnostic uncertainty. These limitations highlight the need for alternative, cost-effective, and non-invasive biomarkers, especially in places like Bangladesh, where resources are limited.

Soluble Axl (sAxl) is the circulating extracellular domain of the Axl receptor tyrosine kinase and has recently emerged as a promising marker for liver cancer. Axl has key roles in cell proliferation, epithelial-mesenchymal transition, and tumor invasion.[16] The cleaved soluble form (sAxl) reflects receptor shedding and correlates with tumor aggressiveness.[17-19]

Although several studies from China, Egypt, and Europe have demonstrated the superior diagnostic performance of sAxl over AFP[15,16,18,19], its clinical utility has not yet been validated in Bangladeshi populations. This study, therefore, aimed to evaluate the diagnostic performance of serum sAxl compared with AFP in differentiating HCC from cirrhosis in Bangladeshi patients.

Methods:

A comparative cross-sectional study was conducted using consecutive sampling in the Departments of Laboratory Medicine and Hepatology, Bangabandhu Sheikh Mujib Medical University, from March 2024 to February 2025. We enrolled 64(sixty-four) participants after IRB approval. Group I (n = 32): HCC with cirrhosis and Group II (n = 32): Cirrhosis without HCC. Clinicians diagnosed cirrhosis using a combination of clinical, biochemical, and imaging findings. They confirmed HCC according to AASLD imaging guidelines or, when necessary, by cytology/biopsy. We excluded patients with malignancies other than HCC or systemic inflammatory diseases.

We collected 5 ml of venous blood after obtaining informed consent, centrifuged it, and stored the serum at –20 °C.We equilibrated all reagents and samples to room temperature before analysis. We placed the required ELISA strips in the plate frame and stored unused strips at 2–8 °C.For each assay, we added 50 µl of standard to designated wells. We added 40 µl of serum sample and 10 µl of anti-sAxl antibody to the sample wells, then 50 µl of streptavidin-HRP to all standard and sample wells except blanks. We sealed and incubated the plate at 37 °C for 60 minutes.After incubation, we washed the wells five times with wash buffer and ensured we removed all fluid between washes. We then added 50 µl each of substrate solutions A and B in sequence, incubated in the dark for 10 minutes at 37 °C, and stopped the reaction with 50 µl of stop solution, which changed the color from blue to yellow.We read optical density (OD) within 10 minutes using a microplate reader set to 450 nm.

We analyzed data using SPSS v26. Continuous variables were summarized as mean ± SD or median (IQR), depending on normality per the Shapiro–Wilk test. Group comparisons used the Mann–Whitney U or Chi-square test. Diagnostic performance was evaluated by ROC curves, reporting AUC, sensitivity, specificity, PPV, NPV, and accuracy values.

Statistical significance was set at $p < 0.05$. We compared AUCs for AFP and sAxl using DeLong's test.

Ethical Considerations

We obtained ethical approval from the IRB of BSMMU (No BSMMU/2024/6695, dated 10/07/2024). We acquired written informed consent from all participants.

Results:

Of 64 participants (32 in each group), the overall mean ± SD age was 53 ± 11 years. Most HCC patients were aged ³61 years (31.2%), while non-HCC cirrhotics clustered in the 46–60 year range (43.7%). Males predominated in both groups (87.5% vs 78.1%). Hepatitis B virus (HBV) infection was the principal etiology (78.1% vs 65.6%), with no significant inter-group differences (p = 0.309). table I

Table I

Demographic and Baseline Characteristics of Study Participants (N=64)

Variable	HCC with cirrhosis, N=32)	Cirrhosis without HCC,N=32)	p-value
Age group (years)			
18–30	3 (9.4%)	2 (6.3%)	
31–45	9 (28.0%)	6 (18.7%)	0.412
46–60	10 (31.4%)	14 (43.7%)	
≥61	10 (31.2%)	10 (31.3%)	
Sex			
Male	28 (87.5%)	25 (78.1%)	0.317
Female	4 (12.5%)	7 (21.9%)	
Etiology			
HBV-positive	25 (78.1%)	21 (65.6%)	
HCV-positive	2 (6.3%)	1 (3.1%)	0.309
Non-viral	5 (15.6%)	10 (31.3%)	

Median serum AFP was significantly higher in HCC patients (100.1 ng/ml) compared with cirrhotic controls (27.9 ng/ml; p < 0.001). Median serum sAxl was also markedly elevated in HCC (146.4 ng/ml) versus cirrhosis (25.6 ng/ml; p < 0.001). Table II

Table II

Serum biomarker levels among study participants (N=64)

Biomarker	HCC with cirrhosis N=32)	Cirrhosis without HCC(N=32)	p-value
Serum AFP (ng/ml)			
Mean ± SD	161.99± 38.68	0.31 ± 719.13	<0.001
Median (IQR)	100.10	27.95	
Serum sAxl (ng/ml)			
Mean ± SD	289.06 ± 39.74	81.91 ± 25.03	<0.001
Median (IQR)	146.35	25.60	

Values are expressed as Mean ± SD and Median (IQR). Mann–Whitney U test applied.

Both markers demonstrated statistically significant discrimination between the two groups (p <0.05). AFP showed modest accuracy with an AUC of 0.689 (SE 0.070), sensitivity 42.9%, and specificity 81.3% at a cut-off value of ≥ 56 ng/ml. In contrast, sAxl achieved a higher AUC of 0.794 (SE 0.057), sensitivity 75%, and specificity 84.4% at ≥77.95 ng/ml, indicating good diagnostic discrimination. Overall accuracy was 81.7% for sAxl compared with 62.1% for AFP. DeLong's test confirmed that the AUC for sAxl was significantly greater than that of AFP (p = 0.018), demonstrating the superior diagnostic performance of sAxl as a biomarker for HCC detection. Table-III

Table III

Comparative diagnostic performance of serum AFP and soluble Axl (sAxl) for detection of hepatocellular carcinoma

Biomarker	AUC	SE	Cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	Accuracy (%)	*p*-value	95% CI (Lower–Upper)
AFP	0.68	0.07	≥56.00	42.9	81.3	62.1	0.024	0.45 – 0.72
sAxl	0.79	0.06	≥77.95	75.0	84.4	81.7	<0.001	0.68 – 0.90

AUC=areaunder ROC curve; SE = standard error.

Figure-1 shows that area Under the Curve (AUC) was 0.689 with a standard error of 0.070. This indicates that the test can significantly differentiate between positive and negative cases, with a p-value of 0.024. The 95% confidence interval for the AUC is from 0.454 to 0.728.

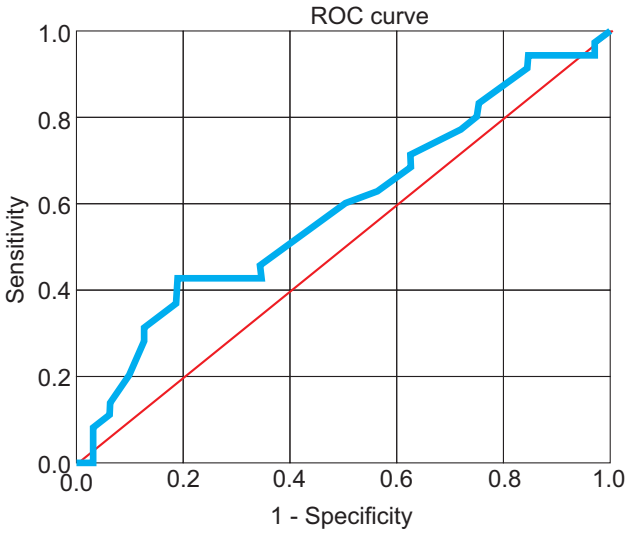

Figure 1. *Receiver operating characteristic (ROC) curves of serum AFP diagnosis of hepatocellular carcinoma.*

Figure-2 shows the area Under the Curve (AUC) of 0.794 with a standard error of 0.057. This result demonstrates a statistically significant ability of the test to differentiate between positive and negative cases, as indicated by a p-value < 0.001. The 95% confidence interval for the AUC ranged from 0.683 to 0.905, suggesting a moderate to high level of accuracy. The AUC value of 0.794 indicates that the test has good discriminatory power.

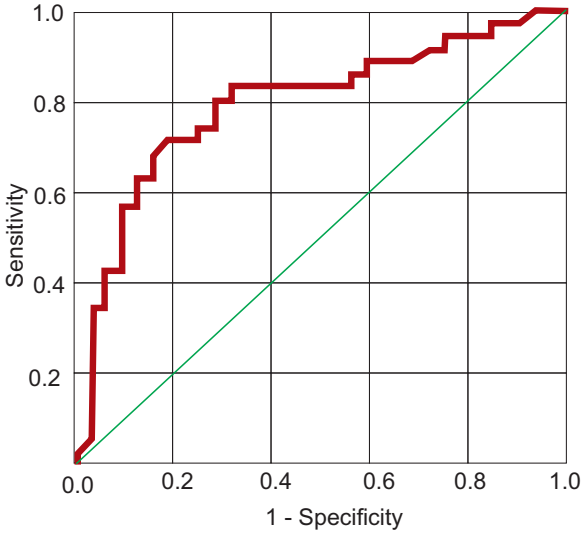

Figure 2. *Receiver operating characteristic (ROC) curves of serum sAxl for diagnosis of hepatocellular carcinoma.*

Patients with HCC had significantly higher serum sAxl levels compared with cirrhotic controls (Mann–Whitney U, $p<0.001$). The correlation coefficient ($r=0.676$) further suggests a strong positive association between higher sAxl levels and HCC status."

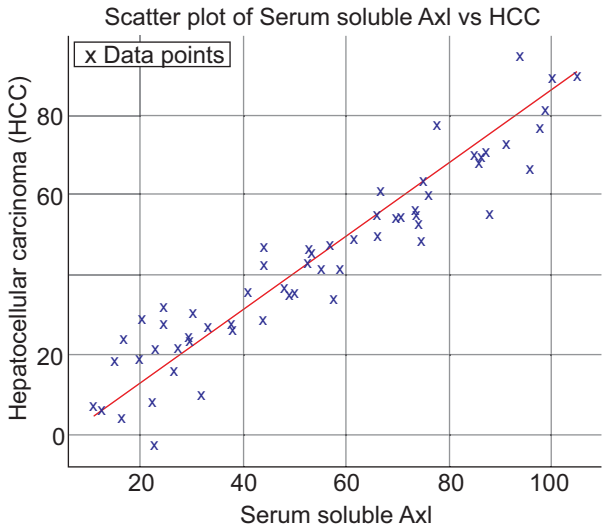

Figure 3. *Association between serum sAxl levels and presence of HCC*

Discussion:

The demographic and etiologic profile of our study participants—predominantly older males with HBV-related liver disease—mirrors national and regional trends.[10,11] HCV infection was infrequent, consistent with previous South Asian data.[12,13] HBV-related cirrhosis remains the predominant substrate for HCC development in Bangladesh, reflecting the high background prevalence of chronic hepatitis B.

Serum AFP continues to play a role as a conventional biomarker for HCC detection; however, its diagnostic accuracy is suboptimal. In our study, AFP yielded an AUC of 0.689 with a sensitivity of 42.9%, which is similar to other studies.[15,16,18] These values underscore its limited sensitivity, particularly for early or small tumors, and its susceptibility to false-positive elevation in cirrhosis or active hepatitis[3,4,15] Hence, reliance on AFP alone may delay diagnosis and limit opportunities for curative intervention.

By contrast, serum sAxl demonstrated superior diagnostic discrimination (AUC 0.794) with balanced sensitivity and specificity (75% and 84.4%, respectively). These results are consistent with studies by Song et al.[15] El Lehleh et al.[16], and Fu et al.[18] which showed comparable or higher diagnostic accuracy in independent cohorts. Mechanistically, Axl receptor activation drives tumor proliferation and invasion; the

soluble form reflects receptor shedding and tumor burden.[19,20] Elevated sAxl levels, therefore, serve as a surrogate for aggressive tumor biology.

Our head-to-head comparison confirmed that sAxl is superior compared to AFP in all diagnostic parameters, including AUC, sensitivity, specificity, and overall accuracy. The difference in AUC between the two biomarkers was statistically significant (p = 0.018, DeLong's test). These findings align with other studies conducted in different parts of the world, suggesting that sAxl can complement or even replace AFP in early HCC detection.[15,16,18,19]

In the Bangladeshi context, sAxl could enhance screening and surveillance programs among high-risk cirrhotic patients. Combining sAxl with AFP may further improve diagnostic sensitivity, supporting earlier detection and treatment.[17,19] Incorporating such biomarkers in surveillance strategies for HCC detection in any cirrhosis patients could be a pragmatic step.

Limitations:

This study was limited by its single-center design and modest sample size, which may restrict generalizability. Histological confirmation was unavailable for some participants. Larger, multicenter, and longitudinal studies are warranted to validate these findings and to explore the potential prognostic value of sAxl for recurrence and survival.

Conclusion:

Serum soluble Axl (sAxl) demonstrated significantly superior diagnostic performance compared with AFP in the diagnosis of HCC from cirrhosis among Bangladeshi patients. These results support sAxl as a promising, non-invasive biomarker for early HCC detection and surveillance.

Recommendations:

Conduct larger multicenter studies to validate sAxl performance across Bangladeshi populations.Explore combined AFP + sAxl algorithms to enhance sensitivity for early HCC. Evaluate sAxl as a prognostic indicator for recurrence and survival. Integrate biomarker-based screening in HBV surveillance programs at the national level.

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