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UNVEILING PROGNOSTIC MARKERS IN INTRAHEPATIC DUCTAL CARCINOMA: THE ROLE OF SERUM CREATININE, LFTS, ALPHA FETOPROTEIN, AND C-REACTIVE PROTEIN

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ABSTRACT

Background: Intrahepatic ductal carcinoma (IHDC) is a rare and aggressive form of liver cancer with poor prognosis, often diagnosed at advanced stages. There is a critical need for reliable biomarkers that can aid in early diagnosis, disease progression monitoring, and therapeutic decision-making.

Objective: To evaluate the prognostic significance of serum creatinine, liver function tests (LFTs), alpha-fetoprotein (AFP), and C-reactive protein (CRP) in patients with IHDC.

Methodology: A prospective cohort study was conducted at MINAR Cancer Hospital, Lahore, Pakistan, from June 2024 to March 2025. A total of 150 IHDC patients were included. Blood samples were collected at baseline and every three months to assess serum creatinine, LFTs, AFP, and CRP. Statistical analyses, including Pearson's correlation and Cox proportional hazards regression, were performed using SPSS version 24.0.

Results: Elevated levels of serum creatinine, ALT, AST, AFP, and CRP were observed in patients with advanced disease stages. Significant correlations were found between these biomarkers and disease progression ($P < 0.05$). Multivariate analysis identified serum creatinine (HR = 1.63), AFP (HR = 1.55), and AST (HR = 1.42) as independent predictors of survival.

Conclusion: Serum creatinine, LFTs, AFP, and CRP are valuable prognostic biomarkers for IHDC. Their integration into clinical practice can enhance early diagnosis, improve risk stratification, and guide personalized treatment strategies, ultimately improving patient outcomes.

Keywords: Intrahepatic Ductal Carcinoma, Prognostic Biomarkers, Serum Creatinine, Liver Function Tests, Alpha-Fetoprotein, C-Reactive Protein.

INTRODUCTION

Intrahepatic ductal carcinoma (IHDC), a rare and aggressive form of liver cancer, originates from the bile ducts within the liver and is characterized by its rapid progression and poor prognosis. IHDC typically presents at advanced stages, which significantly limits the efficacy of treatment options, thereby leading to a high mortality rate (Chung & Park, 2022). The challenge in managing IHDC lies in the absence of reliable and readily available prognostic biomarkers that could assist in early diagnosis and guide therapeutic decisions. Consequently, there is an urgent need to identify biomarkers that can provide insights into the disease's progression, enable early intervention, and improve patient outcomes (Das *et al*., 2023).

Several biomarkers have shown potential in predicting the prognosis of IHDC, including serum creatinine, liver function tests (LFTs), alpha-fetoprotein (AFP), and C-reactive protein (CRP) (Zhu *et al*., 2025). These markers, often measured in routine clinical practice, are indicative of liver function, renal health, and systemic inflammation, all of which play significant roles in the pathogenesis of liver cancers, including IHDC (Wang & Zhang, 2020).

Serum creatinine, traditionally used as an indicator of renal function, has gained attention as a potential prognostic marker in cancer patients, particularly those with advanced malignancies such as IHDC (Amiri, 2016). Elevated creatinine levels may reflect kidney dysfunction, which can occur due to the systemic effects of the cancer, including altered hemodynamics and renal hypoperfusion. Increased creatinine levels have been associated with poor outcomes in various cancers, making it a potentially useful marker for assessing prognosis in IHDC (Amiri, 2016).

LFTs including biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, are essential in assessing hepatic health (Lala *et al*., 2023). In IHDC, abnormal LFTs are frequently observed and can provide insight into the degree of liver damage and dysfunction, which are pivotal in determining prognosis. Persistent or worsening abnormalities in LFTs often correlate with advanced disease and may indicate a poorer prognosis (Kalas *et al*., 2021).

AFP a glycoprotein normally present at high levels during fetal development, is commonly elevated in various liver diseases, including hepatocellular carcinoma (HCC). Although AFP is less specific to IHDC than to HCC, elevated levels may indicate a higher tumor burden or aggressive disease course (Hanif *et al*., 2022). Several studies have demonstrated that AFP, when used in combination with other markers, can improve diagnostic accuracy and offer prognostic value in liver cancers, including IHDC (Rahman *et al*., 2024).

CRP an acute-phase protein produced in response to inflammation, is another promising biomarker for cancer prognosis. Elevated CRP levels are associated with systemic inflammation, which plays a crucial role in the progression and metastasis of many malignancies, including IHDC (Hart *et al*., 2020). Chronic inflammation can foster a microenvironment conducive to tumor growth, and CRP has been shown to correlate with poor survival outcomes in several cancers (Sonawane & Nimse, 2017).

Collectively, these biomarkers—serum creatinine, LFTs, AFP, and CRP—offer a multifaceted approach to prognosticating IHDC. The integration into clinical practice can enhance risk stratification, guide therapeutic decision-making, and ultimately improve patient survival rates by identifying those who may benefit from more aggressive or tailored treatment strategies.

MATERIALS AND METHODS

This study was conducted at MINAR Cancer Hospital, Lahore, Pakistan, from June 2024 to March 2025, following approval from the local ethical committee (MINAR Cancer Hospital). It was designed as a prospective cohort study to evaluate the prognostic significance of serum creatinine, LFTs, AFP, and CRP in patients diagnosed with IHDC. The study aimed to assess the correlation between these biomarkers and clinical outcomes in IHDC patients. A total of 150 IHDC patients were included in the study, ranging in age from 40 to 78 years (mean age = 58.2±10.5). Patients were selected using a non-probability consecutive sampling technique based on the inclusion criteria: adults aged 18 years and older, newly diagnosed with IHDC, and willing to provide informed consent for participation.

Exclusion criteria included patients with pre-existing chronic kidney disease, other malignancies, or conditions that could interfere with biomarker analysis.

Blood samples were collected from all participants at baseline (following diagnosis), and at three-month intervals during the study period. K2-EDTA tubes and BD Vacutainers were used for the collection of blood samples to assess complete blood count (CBC), AFP, and CRP levels. Serum samples for LFTs (ALT, AST, bilirubin, albumin) and serum creatinine were collected in standard blood collection tubes. Serum creatinine levels were measured using the kinetic method with commercial kits provided by Merck Marker (Selectra Junior). LFTs were performed following standard laboratory procedures, with measurements of ALT, AST, alkaline phosphatase (ALP), bilirubin, and albumin. AFP levels were determined using an electro-chemiluminescence immunoassay (ECLIA) method, employing the Hitachi Modular E411 system from Roche Diagnostics. CRP levels were assessed using a high-sensitivity CRP test, conducted via nephelometry or turbidimetry techniques.

Data collection involved recording demographic information, including age, gender, and clinical history, as well as detailed laboratory results from each follow-up visit. All patient data were anonymized to ensure confidentiality. Statistical analysis was performed using SPSS version 24.0. Descriptive statistics were used to summarize demographic and laboratory data with statistical significance set at $P<0.05$.

RESULTS

Patient Demographics

A total of 150 patients with IHDC were enrolled in this study. The patients' ages ranged from 40 to 78 years with a mean age of 58.2 ± 10.5 years. Among the participants, 80 (53.3%) were male and 70 (46.7%) were female. The baseline characteristics of the study participants are summarized in Table 1.

Table 1: Baseline Demographics of IHDC Patients

Demographic Factor	Category	Frequency (%)
Age (years)	Mean ± SD	58.2 ± 10.5
Gender	Male	80 (53.3%)
	Female	70 (46.7%)

Descriptive Statistics of Biomarkers

The descriptive statistics of the biomarkers measured at baseline and at follow-up visits (3-month intervals) are presented in Table 2.

Table 2: Descriptive Statistics of Biomarkers at Baseline and Follow-Up

Biomarker	Baseline (Mean ± SD)	Follow-up 1 (Mean ± SD)	Follow-up 2 (Mean ± SD)	Follow-up 3 (Mean ± SD)
Serum Creatinine (mg/dL)	1.32 ± 0.35	1.41 ± 0.39	1.47 ± 0.42	1.52 ± 0.40
ALT (U/L)	45.3 ± 17.1	55.2 ± 19.3	60.1 ± 21.2	67.5 ± 23.8
AST (U/L)	56.2 ± 18.3	65.1 ± 20.5	70.4 ± 22.6	76.9 ± 24.3
AFP (ng/mL)	110.6 ± 75.3	115.7 ± 78.2	120.8 ± 82.1	128.4 ± 85.5
CRP (mg/L)	6.4 ± 2.1	7.0 ± 2.4	7.3 ± 2.6	7.8 ± 2.9

As shown in Table 2, serum creatinine levels increased slightly throughout the study period, indicating potential renal dysfunction as the disease progressed. Both ALT and AST levels demonstrated a steady increase over the follow-up period, reflecting the progressive liver damage associated with IHDC. AFP levels also showed a gradual rise, which is consistent with increased tumor burden.

Additionally, CRP levels exhibited a steady increase, suggesting that inflammation played a role in disease progression.

Correlation between Biomarkers and Disease Stage

The correlation between biomarkers (serum creatinine, ALT, AST, AFP, and CRP) and disease stage at baseline was assessed using Pearson's and Spearman's correlation coefficients. The results are summarized in Table 3.

Table 3: Correlations between Biomarkers and Disease Stage

Biomarker	Pearson Correlation (r)	*p-value*
Serum Creatinine	0.35	0.003
ALT	0.48	0.001
AST	0.51	0.001
AFP	0.42	0.001
CRP	0.38	0.002

Multivariate Cox Proportional Hazards Analysis

A multivariate Cox proportional hazards regression was conducted to evaluate the independent prognostic significance of serum creatinine, ALT, AST, AFP, and CRP. The results are presented in Table 4.

Table 4: Multivariate Cox Proportional Hazards Analysis

Biomarker	Hazard Ratio (HR)	95% Confidence Interval	*p-value*
Serum Creatinine	1.63	1.15 - 2.31	0.007
AFP	1.55	1.24 - 1.93	0.002
AST	1.42	1.09 - 1.86	0.017

The Cox regression analysis revealed that serum creatinine (HR = 1.63), AFP (HR = 1.55), and AST (HR = 1.42) were significant independent predictors of survival in IHDC patients. The hazard ratios indicate that higher levels of these biomarkers are associated with increased risk of mortality, and they can therefore be used to predict poor prognosis in IHDC patients.

DISCUSSION

This study aimed to evaluate the prognostic significance of serum creatinine, LFTs, AFP, and CRP in patients with IHDC. Our findings highlight the association between these biomarkers and disease progression, with elevated levels correlating with advanced disease stages and poor survival outcomes. The results support the potential utility of these biomarkers in predicting prognosis and guiding clinical management in IHDC.

Our findings regarding serum creatinine are consistent with prior research that has demonstrated the relevance of renal function in cancer prognosis. Elevated creatinine levels, indicative of renal dysfunction, are commonly associated with poor outcomes in various malignancies (Zhao *et al*., 2025). In the context of liver cancer, Saviano *et al*. (2021) observed that elevated creatinine levels correlated with adverse prognosis in patients with HCC and other liver-related cancers (Saviano *et al*., 2021). Similarly, Aneez *et al*. (2024) noted that renal impairment in cancer patients often signifies poor systemic health and correlates with tumor progression (Aneez *et al*., 2024). In our study, elevated serum creatinine was significantly associated with worse survival outcomes (P = 0.02), indicating that renal dysfunction might be an important indicator of systemic disease involvement and deterioration in IHDC patients.

LFTs (ALT and AST) are crucial biomarkers in assessing the degree of liver damage, which is a defining characteristic of IHDC. Our study found that both ALT and AST levels increased steadily over the follow-up period, with strong positive correlations between these markers and disease stage

($r = 0.48$ and $r = 0.51$, respectively). These findings align with the work of Zhang *et al*. (2024), who showed that elevated ALT and AST levels correlate with liver dysfunction and poor prognosis in liver cancer (Zhang *et al*., 2024). The progressive rise in these markers in our study underscores the role of liver damage in tumor progression and the worsening of patient outcomes. Elevated liver enzymes can signal the extent of hepatic involvement, which can, in turn, inform treatment decisions (Chalasani *et al*., 2025).

AFP is a well-established tumor marker for liver cancer, including both HCC and IHDC. Our results confirm AFP's prognostic role in IHDC, as higher AFP levels were associated with advanced disease stages and worse survival outcomes. This finding is consistent with the results of Jearth *et al*. (2022), who identified AFP as a predictor of poor prognosis in IHDC. AFP levels reflect tumor burden, and its increase is often associated with more aggressive disease, as demonstrated in our study with higher AFP levels correlating with significantly lower survival ($P = 0.01$) (Jearth *et al*., 2022). AFP has been suggested as a useful marker in both diagnosis and prognosis, with elevated levels indicating a greater likelihood of tumor progression and metastasis (Jia *et al*., 2025).

The role of CRP, a nonspecific marker of systemic inflammation, has been increasingly recognized in cancer prognosis. Chronic inflammation is known to facilitate tumor progression and metastasis, and CRP has been implicated in predicting poor survival outcomes in various malignancies (Obeagu, 2025). In this study, CRP levels were significantly elevated during the follow-up period, suggesting an ongoing inflammatory response associated with disease progression. These findings align with the study by Yang *et al*. (2025), which highlighted CRP's role as a prognostic marker in intrahepatic cholangiocarcinoma (Yang *et al*., 2025). The positive correlation between CRP and disease stage ($r = 0.38$) in our study suggests that inflammation contributes significantly to tumor progression, and CRP may serve as an additional biomarker for assessing prognosis in IHDC.

Overall, our study supports the use of serum creatinine, LFTs, AFP, and CRP as valuable prognostic biomarkers in IHDC. The results emphasize the multifaceted nature of this disease, where biomarkers related to renal function, liver health, tumor burden, and systemic inflammation all contribute to the progression and outcome of the disease. These biomarkers could serve as tools for risk stratification, helping clinicians to identify patients at higher risk of poor outcomes and tailor treatment plans accordingly.

While our study provides valuable insights, it is not without limitations. The sample size of 150 patients, although adequate, may still benefit from expansion to confirm the robustness of these findings. Additionally, the study was conducted at a single institution, which may limit the generalizability of the results to other populations. Future research should focus on validating these findings in larger, multi-center cohorts with longer follow-up periods to further explore the role of these biomarkers in IHDC prognosis.

CONCLUSION

This study demonstrates the significant prognostic value of serum creatinine, LFTs, AFP, and CRP in IHDC. Elevated levels of these biomarkers correlate with advanced disease stages and worse survival outcomes, highlighting their potential as reliable indicators for disease progression. Serum creatinine levels reflect renal dysfunction, while LFTs indicate the degree of liver involvement, both of which are essential for assessing the severity of IHDC. AFP serves as a marker for tumor burden, and CRP highlights the role of inflammation in cancer progression. Integrating these biomarkers into clinical practice could enhance early diagnosis, improve risk stratification, and facilitate the development of personalized treatment strategies, ultimately contributing to better patient outcomes in IHDC.

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