DOI: https://doi.org/10.54393/pjhs.v7i5.3685

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 7, Issue 05 (May 2026)

Original Article

OPEN ACCESS

Association of Blood Baseline Parameters with Alpha-Fetoprotein and Its Importance as a Prognostic Factor in Intrahepatic Ductal Carcinoma Patients: An Analytical Cross-Sectional Study

Beenish Haleem Riaz[1], Khalida Anwar[2], Madeeha Mushtaq[3], Kamran Shauket[4], Ayesha Khan[5], Abeerah Zafar[6], Rubaida Mehmood[7], Tayyaba Yasin[8*], Ayesha Arif[9] and Hina Awais[8]

[1]Department of Biochemistry, Nawaz Sharif Medical College, Gujrat, Pakistan
[2]Department of Biochemistry, Rahim Yar Khan Medical and Dental College, Rahim Yar Khan, Pakistan
[3]Department of Biochemistry, University of Health Sciences, Lahore, Pakistan
[4]Department of Medicine, Sahiwal Teaching Hospital, Sahiwal, Pakistan
[5]Department of Biochemistry, Rashid Latif Medical College, Lahore, Pakistan
[6]Department of Gynecology and Obstetrics, Sahiwal Teaching Hospital, Sahiwal, Pakistan
[7]Department of Diagnostic Lab, Multan Institute of Nuclear Medicine and Radiotherapy, Pakistan Atomic Energy Commission, Multan, Pakistan
[8]Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[9]Department of Health Promotion, University of Palermo, Palermo, Italy

ARTICLE INFO

Keywords:
Intrahepatic Ductal Carcinoma, Alpha-Fetoprotein, Liver Function Tests, Complete Blood Count, Serum Creatinine, Prognostic Biomarkers

How to Cite:
Riaz, B. H., Anwar, K., Mushtaq, M., Shauket, K., Khan, A., Zafar, A., Mehmood, R., Yasin, T., Arif, A., & Awais, H. (2026). Association of Blood Baseline Parameters with Alpha-Fetoprotein and Its Importance as a Prognostic Factor in Intrahepatic Ductal Carcinoma Patients: An Analytical Cross-Sectional Study: Blood Parameters and AFP as Prognostic Markers in Intrahepatic Ductal Carcinoma. Pakistan Journal of Health Sciences, 7(5), 104-109. https://doi.org/10.54393/pjhs.v7i5.3685

***Corresponding Author:**
Tayyaba Yasin
Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples, Italy
tayybayasin1122@gmail.com

Received Date: 13th December, 2025
1st Revision Received: 25th February, 2026
2nd Revision Received: 5th March, 2026
Acceptance Date: 19th March, 2026
Published Date: 31st May, 2026

ABSTRACT

Intrahepatic Ductal Carcinoma (IHDC), a subtype of cholangiocarcinoma, is an aggressive liver cancer with a poor prognosis and rising global incidence. Although Alpha-Fetoprotein (AFP) is a common tumor biomarker, its prognostic value in IHDC is limited when used alone. **Objectives:** To determine the association between AFP and blood baseline parameters to evaluate their combined prognostic significance in patients with IHDC. **Methods:** This analytical cross-sectional study was conducted at MINAR Cancer Hospital, Multan, Pakistan, from January 2019 to December 2020. A total of 107 histologically confirmed IHDC patients (61 males, 46 females; mean age = 56.8 ± 11.2 years) were included. CBC, LFTs, and serum creatinine were analyzed using standard automated methods, while AFP was measured via electro-chemiluminescence immunoassay (ECLIA). Data were analyzed using SPSS version 24.0. **Results:** Significant gender-based differences were found in eosinophil counts ($p = 0.041$) and serum creatinine ($p = 0.024$). Elderly patients (≥60 years) showed higher monocytes ($p=0.030$) and Mean Platelet Volume ($p=0.002$). Across tumor stages, neutrophils increased (66.8% → 78.2%, $p<0.001$), lymphocytes decreased (25.1% → 18.5%, $p < 0.001$), and ALP and bilirubin rose significantly ($p = 0.021$; $p=0.008$). AFP correlated positively with ALP ($r=0.85$), SGOT ($r=0.79$), bilirubin ($r=0.86$), serum creatinine ($r=0.99$), and blood urea ($r=0.98$), and negatively with lymphocytes ($r = -0.83$). **Conclusions:** AFP was associated with hepatic, renal, and inflammatory parameters in IHDC, suggesting its potential as a composite biomarker for staging and prognosis.

INTRODUCTION

Liver cancer is among the most common and deadliest malignancies occurring all over the world, as it is the third most common cause of cancer deaths globally. The GLOBOCAN 2022 estimates that liver cancer has more than 905,000 new cases and 830,000 deaths each year, making it a serious issue of global health concern [1]. Intrahepatic ductal carcinoma (IHDC), a subtype of cholangiocarcinoma, has gained growing clinical interest because of its

DOI: https://doi.org/10.54393/pjhs.v7i5.3685

aggressive pathophysiology, complicated diagnosis, and unfavorable prognosis [2]. IHDC is a complication of the epithelial cells of the intrahepatic biliary ducts that normally occurs at an advanced stage and thus limits the treatment modalities and survival rates [3]. The world has witnessed a significant increase in IHDC cases in the last thirty years, with 165 percent reported in the United States only. This has been observed to be similar in trends in Japan, the United Kingdom, and various areas in Europe, which demonstrates a shift in epidemiology across the globe [4]. The etiology of IHDC is multifactorial, and it includes chronic inflammation of the biliary tract, liver cirrhosis and fibrosis, viral hepatitis (especially hepatitis B and C), and exposure to environmental toxins [5]. Liver cancer is an emerging societal burden in Pakistan. The estimates presented by the Pakistan Medical Research Council and WHO show that liver cancer is among the five leading malignancies in the country [6]. The high rate of hepatitis B and C infections, extensive liver fibrosis, and inaccessibility to screening programs play a major role in the increased incidence of hepatocellular carcinoma (HCC) and IHDC [7]. Investigations conducted at tertiary care hospitals in Karachi, Lahore, and Islamabad have already shown that cholangiocarcinoma is occurring at an accelerating rate, and thus necessitating the implementation of superior prognostic and diagnostic methods [8, 9]. IHDC has no specific clinical manifestations but rather vague symptoms, including pain in the abdomen, jaundice, weight loss, and fatigue, thus making it difficult to diagnose. Alpha-Fetoprotein (AFP), Liver Function Tests (LFTs), and Serum Creatinine are also some of the extensively researched biochemical markers that could be used in the diagnosis and prognosis of the disease. High AFP concentrations are typically found in hepatobiliary tumors such as IHDC, and these levels indicate aggressiveness of the tumor, lack of differentiation, and high-stage disease [10]. But AFP is not sensitive and specific enough to be used as an independent marker. Thus, the integration of AFP with other biochemical and hematological data, including Complete Blood Count (CBC) indices, LFTs, and serum creatinine, can be a more accurate predictive model [11]. Recent studies in the world indicate that the deviations in the factors of the CBC, such as high red cell distribution width (RDW), changed platelet count, and high neutrophil-to-lymphocyte ratio (NLR), are linked to worse survival rates in IHDC [12]. Equally, high alkaline phosphatase (ALP), bilirubin, and AST/ALT ratios on LFTs are associated with obstruction of the bile ducts, hepatic dysfunction, and tumor load. Though serum creatinine is a classical indication of renal function, it can also signify systemic use and metabolic stress in liver malignancies [13]. Although there are limited studies that have evaluated the prognostic power of AFP, CBC, LFTs, and serum creatinine integrated in Pakistani IHDC patients, the predisposing conditions of the hepatic are highly prevalent [14].

Despite the recognized role of alpha-fetoprotein (AFP) in liver malignancies, limited data exist on its relationship with baseline hematological, hepatic, and renal parameters in intrahepatic ductal carcinoma (IHDC) patients. This gap hampers the understanding of AFP's prognostic potential when integrated with routine blood and biochemical markers. Therefore, the present study aimed to evaluate the association of serum AFP with CBC, liver function, and renal indices, and to explore its utility as a prognostic factor in relation to tumor stage and grade in IHDC patients.

METHODS

A descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Mohtarma Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur, AJ and K, after taking the ethical approval (REF. NO 10/Academic Block Trauma centre/Surgery/2025) from February 2025 to August 2025. The sample size was 151, keeping the frequency of HELLP syndrome in thrombocytopenia patients as 11% based on a previous study, confidence level being 95%, and margin of error 5% under the WHO sample size calculation formula [8]. All the patients were enrolled by using a consecutive sampling technique, all women having age of 18-40 years with singleton pregnancy and women with thrombocytopenia were included in this study and the bleeding disorder other than thrombocytopenia on medical records and history, already taking antihypertensive medication on history, diabetes mellitus, HIV on history and medical records and multiple pregnancies on ultrasound were excluded. All the pregnant women who met the inclusion criteria were invited to take part in the study and were admitted to the ward following OPD inclusion. All the patients were informed about the purpose and benefits of the study and assured that the study is conducted with the sole purpose of research and publication of data, and given a written informed consent in case they agreed. After taking a complete history and baseline investigation, a 5ml blood sample was obtained and sent to the laboratory to confirm thrombocytopenia. The level of thrombocytopenia was defined based on the number of platelets in the body as mild (100150 ×10 09/L), moderate (5099 ×10 09/L), and severe (50 09/L) [11]. After confirmation, women and neonates were followed till delivery to detect preeclampsia, HELLP syndrome, placental abruption, preterm birth, and low birth weight. Preeclampsia had been categorized as new-onset hypertension (140/90mmHg or higher on two occasions

DOI: https://doi.org/10.54393/pjhs.v7i5.3685

after 20 weeks of pregnancy) with proteinuria (300 mg/24h or above) or end-organ dysfunction. The HELLP syndrome was diagnosed on the grounds of hemolysis, increased liver enzymes, and reduced platelet count. Preterm birth entailed a birth that was less than 37 weeks of gestational age. Low birth weight was considered as a birth weight of the neonate that was less than 2500 g, irrespective of gestational age [12]. All the above-mentioned information was recorded on a pre-designed proforma.

Data analysis was done with the help of SPSS software (version 25.0). All continuous variables like age, BMI, platelet count, and gestational age were shown as mean ± standard deviation (SD), and categorical variables like preeclampsia, placental abruption, HELLP syndrome, preterm birth, and low birth weight were presented as frequency and percentage. Fetomaternal outcome was stratified according to the severity of thrombocytopenia. After stratification, the chi-square test/Fisher Exact test was considered a P value ≤ 0.005 as significant.

RESULTS

A total of 107 patients diagnosed with IHDC were analyzed. Participants' ages ranged from 39 to 76 years (mean ± SD=56.8 ± 11.2 years). Of these, 61 (57%) were male, and 46 (43%) were female (Table 1).

Table 1: Baseline Characteristics of IHDC Patients (n=107)

Variables	Categories	Frequency (%)	Mean ± SD
Age (Years)	–	–	56.8 ± 11.2
	< 60 years	64 (59.8%)	–
	≥ 60 years	43 (40.2%)	–
Gender	Male	61 (57.0%)	–
	Female	46 (43.0%)	–
Tumor Grade	II	38 (35.5%)	–
	III	45 (42.1%)	–
	IV	24 (22.4%)	–
Cancer Stage	II	29 (27.1%)	–
	III	48 (44.9%)	–
	IV	30 (28.0%)	–

Gender-based comparisons revealed significant differences in eosinophil counts (p=0.041) and serum creatinine levels (p=0.024), with males exhibiting slightly higher mean values. Among geriatric patients, Mean Platelet Volume (MPV) (p=0.002) and monocyte count (p=0.030) differed significantly from those of younger patients (Table 2).

Table 2: Comparison of Hematological and Biochemical Parameters by Gender and Age Group

Parameters	Male (Mean ± SD)	Female (Mean ± SD)	p-value[a]	<60 years (Mean ± SD)	≥60 years (Mean ± SD)	p-value[a]
Neutrophils (%)	72.1 ± 9.6	70.4 ± 8.8	0.281[a]	71.5 ± 8.9	72.9 ± 9.3	0.468[a]
Lymphocytes (%)	21.4 ± 7.5	22.2 ± 6.9	0.573[a]	22.8 ± 7.0	20.5 ± 7.6	0.152[a]
Monocytes (%)	5.1 ± 1.3	5.3 ± 1.4	0.417[a]	4.8 ± 1.2	5.7 ± 1.5	0.030*[a]
Eosinophils (%)	3.9 ± 1.5	2.8 ± 1.3	0.041*[a]	3.1 ± 1.4	3.6 ± 1.7	0.209[a]
Platelets ($\times 10^9$/L)	246.8 ± 75.5	258.2 ± 79.1	0.482[a]	250.6 ± 70.4	254.9 ± 83.7	0.714[a]
MPV (fL)	9.6 ± 1.1	9.8 ± 1.2	0.364[a]	9.2 ± 0.9	10.3 ± 1.0	0.002*[a]
ALP (U/L)	283.7 ± 95.2	275.1 ± 88.3	0.643[a]	278.6 ± 92.4	281.9 ± 94.7	0.827[a]
Serum Creatinine (mg/dL)	1.28 ± 0.34	1.09 ± 0.29	0.024*[a]	1.19 ± 0.33	1.22 ± 0.31	0.574[a]

[a]Independent sample Student's t-test
*Statistically significant at p<0.005

Significant changes in neutrophil, lymphocyte, and ALP levels were observed across cancer stages and grades. Patients with stage IV disease showed markedly elevated neutrophil counts (p<0.001) and ALP levels (p=0.021) compared to lower stages. Similarly, lymphopenia was more pronounced in advanced stages and higher grades (Table 3).

Table 3: Comparison of Hematological and Biochemical Markers Across Tumor Stage and Grade

Parameters	Stage II	Stage III	Stage IV	p-value[b]	Grade II	Grade III	Grade IV	p-value[b]
Neutrophils	66.8 ± 8.1	72.4 ± 7.5	78.2 ± 9.0	<0.001*[b]	68.7 ± 8.3	73.6 ± 8.0	77.9 ± 9.1	0.030*[b]
Lymphocytes (%)	25.1 ± 6.4	21.3 ± 6.7	18.5 ± 7.1	<0.001*[b]	24.2 ± 6.3	21.1 ± 6.9	18.7 ± 7.0	0.032*[b]
ALP (U/L)	255.6 ± 82.5	282.3 ± 90.7	315.8 ± 98.4	0.021*[b]	248.4 ± 77.2	286.6 ± 91.5	309.3 ± 94.1	0.063[b]
Bilirubin (mg/dL)	1.2 ± 0.4	1.5 ± 0.5	1.9 ± 0.7	0.008*[b]	1.3 ± 0.4	1.5 ± 0.5	1.8 ± 0.6	0.016*[b]

[b]One-way ANOVA
*Statistically significant at p<0.005

Correlation analyses using Pearson's and Spearman's coefficients showed distinct relationships between AFP and several laboratory markers. While no significant correlations were observed with CBC parameters in gender or age subgroups, several associations emerged when stratified by tumor grade and stage. Stage II: AFP correlated strongly with RDW-CV (r=0.91, p=0.03). Stage IV: AFP correlated significantly with platelet count (r=0.56, p=0.010) and plateletcrit (r=0.58, p=0.020).

DOI: https://doi.org/10.54393/pjhs.v7i5.3685

Grade II: Strong correlations were found with WBC (r=0.82, p=0.02) and neutrophils (r=0.88, p=0.010). Grade IV: AFP correlated negatively with lymphocytes (r = –0.83, p=0.030) and positively with ALP (r=0.85, p=0.020), (serum glutamic-oxaloacetic transaminase) SGOT (r=0.79, p=0.030), and bilirubin (r=0.86, p=0.020) (Table 4).

Table 4: Correlation of AFP with Hematological and Biochemical Parameters

Parameters	r-value	p-value[c]
WBC	0.82	0.020*[c]
RDW-CV	0.91	0.030*[c]
Platelets	0.56	0.010*[c]
PCT	0.58	0.020*[c]
Neutrophils	0.88	0.010*[c]
Lymphocytes	–0.83	0.030*[c]
ALP	0.85	0.020*[c]
SGOT	0.47	0.030*[c]
Bilirubin	0.52	<0.001*[c]
Blood Urea	0.98	<0.001*[c]
Serum Creatinine	0.99	<0.001*[c]

[c]Pearson correlation coefficient
*Statistically significant at p<0.005

ROC analysis demonstrated that AFP had an area under the curve (AUC) of 0.76 (95% CI: 0.67–0.84, p < 0.001) for predicting advanced-stage IHDC (Figure 1). At an optimal cutoff value of 220 ng/mL, AFP showed a sensitivity of 72% and specificity of 65% (Table 5).

Table 5: ROC Analysis of AFP for Predicting Advanced-Stage IHDC

Variable	AUC	95% CI	Cutoff	Sensitivity	Specificity	p-value
AFP	0.76	0.67–0.84	220 ng/mL	72%	65%	<0.001*

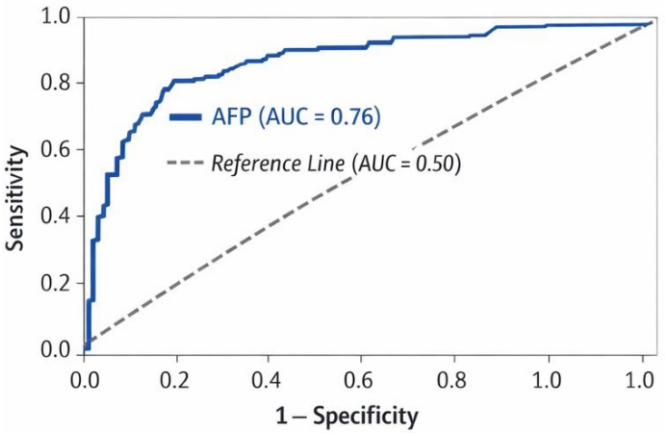

Figure 1: ROC Curve for AFP

DISCUSSION

This study investigated the correlation between AFP and baseline hematological, hepatic, and renal parameters in patients with IHDC to determine their prognostic value. These findings showed significant correlations between AFP and LFTs, especially ALP, SGOT, and bilirubin parameters, as well as hematological ones, including neutrophils and lymphocytes, and renal parameters, including urea and creatinine. These results support the role of AFP as a secondary prognostic biomarker in IHDC. Our mean age of patients was 56.8 and 11.2 years, which is similar to what Fu *et al.* stated, 57.4 and 10.6 years as the mean age of 132 patients with IHDC in China, and Hassan *et al.* found 58 and 9.4 years as the mean age of 50 patients with cholangiocarcinoma in Pakistan [15, 16]. Significantly higher serum creatinine levels in males (1.28 ± 0.34 mg/dL) compared to females (1.09 ± 0.29 mg/dL, p=0.024) are consistent with Chen *et al.* who found values of 1.32 ± 0.41 mg/dL in males versus 1.10 ± 0.33 mg/dL in females (p=0.03) [17]. These increases can indicate premature hepatorenal dysfunction as a result of chronic cholestasis or bile ductal blockage. The larger eosinophil percentage in males (3.9 ± 1.5) is consistent with Taylor *et al.* finding of 3.7 ± 1.4% in males and 2.9 ± 1.3 in females, indicating inflammatory cell activation is associated with cytokine activity of the tumor microenvironment [18]. Among elderly patients (≥60 years), we observed increased monocytes (5.7 ± 1.5%) and Mean Platelet Volume (MPV) (10.3 ± 1.0 fL) compared to younger individuals (4.8 ± 1.2% and 9.2 ± 0.9 fL, respectively, p=0.002). Beudeker *et al.* found the same results and reported MPV of 10.5 ± 1.1 fL and monocytes of 5.8 1.4% in older patients with IHDC [19]. High MPV and monocyte levels are the signs of chronic inflammation and tumor-related activation of macrophages, which are not associated with good prognoses. Upon stratification according to the cancer stage, our records indicated progressive neutrophilia and lymphopenia as the disease progressed. Neutrophils increased from 66.8 ± 8.1% in stage II to 78.2 ± 9.0% in stage IV (p<0.001), while lymphocytes declined from 25.1 ± 6.4% to 18.5 ± 7.1% (p<0.001). Ji *et al.* also provided the median neutrophil and lymphocyte percentages of 74.3 ± 10.2 and 19.7 ± 6.5, respectively, among biliary cancers in the advanced stage and found an NLR of over 4.0 as a predictor of poor survival [20]. As well, in current research, we identified higher ALP (255.6 ± 82.5 U/L vs. 315.8 ± 98.4 U/L, p = 0.021) and total bilirubin (1.2 ± 0.4 vs. 1.9 ± 0.7mg/dL, p=0.008) in the second and fourth stages. Similar biochemical changes were observed by Wang *et al.* reported that ALP 310 (202102) and bilirubin 1.8 (202102) in the end-stage IHDC, with a prominent emphasis on the cholestatic injury and hepatic dysfunction, were used as the prognostic factors [21]. One major result of this study is that AFP is closely positively correlated with ALP (r=0.85, p=0.020), SGOT (r=0.79, p=0.030), and total bilirubin (r=0.86, p=0.020). These results closely resemble those of Chicco *et al.* who observed AFP–ALP correlation (r=0.72, p = 0.010) and AFP–bilirubin correlation (r=0.69, p=0.020) among 92 IHDC

DOI: https://doi.org/10.54393/pjhs.v7i5.3685

patients [22]. In the same way, Ali *et al.* in Pakistan found that the AFP is associated with cholestatic injury and tumor burden because of correlations with AFP and ALP ($r=0.80$, $p<0.01$) and bilirubin ($r=0.77$, $p<0.05$) [23]. We further had a strong correlation between AFP and renal indices, serum creatinine ($r=0.99$, $p<0.001$), and blood urea ($r=0.98$, $p<0.001$), which is similar to Das *et al.* who showed the existence of AFP-creatinine correlation ($r=0.94$, $p<0.001$) in hepatic malignancies associated with hepatorenal syndrome [24]. Such results indicate that AFP could have an indirect relationship with renal failure that results from tumor progression or paraneoplastic nephropathy. The relationship between AFP and neutrophils ($r=0.88$, $p=0.010$) and WBC ($r=0.82$, $p=0.020$) was found to be positive, and it shows that AFP is produced because of inflammation. Similar results were obtained by Yap *et al.* who revealed that high AFP levels were coupled with neutrophil-induced cytokine release (IL-6, TNF-), which correlates with poor survival in cholangiocarcinoma [25]. In contrast, it is also negative and related to the lymphocytes ($r = -0.83$, $p=0.03$) in disease grade IV, which is appropriate since Blanco et al. (2025) reported a mean lymphocyte count of 17.9 ± 6.8 in advanced biliary tumors, highlighting immune exhaustion in advanced tumors [26]. The mean ALP (283.7 ± 95.2 U/L) and mean AFP (247.4 ± 110.6 ng/mL) in this study parallel Munir *et al.* who reported AFP of 236.8 ± 104.5 ng/mL and ALP of 295 ± 88 U/L in hepatobiliary malignancies at AFIP, Rawalpindi [27].

These uniform biochemical trends in the literature demonstrate the prognostic interaction of the AFP and hepatic enzymes. This study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. The lack of survival follow-up restricts causal and long-term prognostic interpretations. Larger multicenter prospective studies are needed to validate these results.

CONCLUSIONS

This study shows that AFP has high correlations with liver enzymes (ALP, SGOT, bilirubin), hematological indices (neutrophils, lymphocytes), and renal function indices (urea, creatinine) in patients with IHDC. The findings are that AFP in combination with CBC, LFT, and renal parameters can be used as a composite prognostic variable, which represents the tumor burden, hepatic damage, and systemic inflammation. Combining AFP and baseline laboratory profiles could thus improve the functioning of IHDC disease monitoring and prognostic accuracy.

Authors' Contribution

Conceptualization: BHR, RM
Methodology: RM
Formal analysis: KS, AK, AZ, AA
Writing and Drafting: KA, MM, TY, HA
Review and Editing: BHR, KA, MM, KS, AZ, RM, TY, HA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Guo Q, Zhu X, Beeraka NM, Zhao R, Li S, Li F *et al.* Projected Epidemiological Trends and Burden of Liver Cancer by 2040 Based on GBD, CI5plus, and WHO data. Scientific Reports. 2024 Nov; 14(1): 28131. doi: 10.1038/s41598-024-77658-2.

[2] Chung T and Park YN. Up-to-date Pathologic Classification and Molecular Characteristics of Intrahepatic Cholangiocarcinoma. Frontiers in medicine. 2022 Mar; 9: 857140. doi: 10.3389/fmed.2022.857140.

[3] Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, Lind GE, Folseraas T, Forbes SJ, Fouassier L, Geier A. Cholangiocarcinoma: Current Knowledge and Future Perspectives Consensus Statement from the European Network for the Study of Cholangiocarcinoma. Nature Reviews Gastroenterology and Hepatology. 2016 May; 13(5): 261-280. doi: 10.1038/nrgastro.2016.51.

[4] Rodrigues PM, Olaizola P, Paiva NA, Olaizola I, Agirre-Lizaso A, Landa A *et al.* Pathogenesis of Cholangiocarcinoma. Annual Review of Pathology: Mechanisms of Disease. 2021 Jan; 16(1): 433-463. doi: 10.1146/annurev-pathol-030220-020455.

[5] Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis, and Treatment Response Assessment. Cells. 2020 Jun; 9(6): 1370. doi: 10.3390/cells9061370.

[6] Ali F, Hussain S, Memon SA, Iqbal SS. Recently, the Top Trending Cancers in a Tertiary Cancer Hospital in Pakistan. Dr. Sulaiman Al Habib Medical Journal. 2023 Jun; 5(2): 42-49. doi: 10.1007/s44229-023-00028-z.

[7] Singal AG, Kanwal F, Llovet JM. Global Trends in Hepatocellular Carcinoma Epidemiology: Implications for Screening, Prevention, and Therapy. Nature reviews Clinical oncology. 2023 Dec; 20(12): 864-884. doi: 10.1038/s41571-023-00825-3.

DOI: https://doi.org/10.54393/pjhs.v7i5.3685

[8] Gatto M, Bragazzi MC, Semeraro R, Napoli C, Gentile R, Torrice A *et al.* Cholangiocarcinoma: update and future perspectives. Digestive and Liver Disease. 2010 Apr; 42(4): 253-260. doi: 10.1016/j.dld.2009.12.008.

[9] Dar FS, Abbas Z, Ahmed I, Atique M, Aujla UI, Azeemuddin M *et al.* National Guidelines for the Diagnosis and Treatment of Hilar Cholangiocarcinoma. World Journal of Gastroenterology. 2024 Mar; 30(9): 1018. doi: 10.3748/wjg.v30.i9.1018.

[10] Wong RJ, Ahmed A, Gish RG. Elevated Alpha-Fetoprotein: Differential Diagnosis-Hepatocellular Carcinoma and Other Disorders. Clinics in Liver Disease. 2015 May; 19(2): 309-323. doi: 10.1016/j.cld.2015.01.005.

[11] Wei Z, Zhang Y, Lu H, Ying J, Zhao H, Cai J. Serum Alpha-Fetoprotein as a Predictive Biomarker for Tissue Alpha-Fetoprotein Status and Prognosis in Patients with Hepatocellular Carcinoma. Translational Cancer Research. 2022 Apr; 11(4): 669. doi: 10.21037/tcr-21-2334.

[12] Shukla R, Silvanus V, Dahal S, Sitaula P, Niraula Z, Gupta CK *et al.* Complete Blood Count-Derived Indices at Admission and Short-Term Outcomes in Intensive Care Unit Patients: A Retrospective Study. Annals of Medicine. 2025 Dec; 57(1): 2522963. doi: 10.1080/07853890.2025.2522963.

[13] Liu D, Heij LR, Czigany Z, Dahl E, Dulk MD, Lang SA *et al.* The Prognostic Value of Neutrophil-To-Lymphocyte Ratio in Cholangiocarcinoma: A Systematic Review and Meta-Analysis. Scientific Reports. 2022 Jul; 12(1): 12691. doi: 10.1038/s41598-022-16727-w.

[14] Hashmi M, Haider G, Danish M, Hassan A, Irshad R, Khalil A. Raised Alpha-Fetoprotein Level and Its Association with Hepatocellular Carcinoma. Pakistan Armed Forces Medical Journal. 2023 Oct; 73(5): 1257. doi: 10.51253/pafmj.v73i5.5419.

[15] Fu X, Wang J, Jiang S, Wu J, Mu Z, Tang Y *et al.* Mortality Trend Analysis of Ischemic Heart Disease in China Between 2010 and 2019: A Joinpoint Analysis. BioMed Central Public Health. 2023 Apr; 23(1): 644. doi: 10.1186/s12889-023-15549-3.

[16] Hassan S, Khan S, Khan A, Khattak M, Khattak EK, Farrukh AM *et al.* Assessment of Liver Transplant Eligibility in Chronic Liver Disease Patients: A Cross-Sectional Study from a Tertiary Care Hospital of Pakistan. Cureus. 2024 May; 16(5): 1-6. doi: 10.7759/cureus.61028.

[17] Chen J, Li K, Shao J, Lai Z, Feng Y, Liu B. The Correlation of Apolipoprotein B With Alterations in Specific Fat Depot Content in Adults. International Journal of Molecular Sciences. 2023 Mar; 24(7): 6310. doi: 10.3390/ijms24076310.

[18] Taylor C, Cheema AS, Asleh K, Finn N, Abdelsalam M, Ouellette RJ. Sex-Specific Cytokine Signatures as Predictors of Anti-PD1 Therapy Response in Non-Small Cell Lung Cancer. Frontiers in Immunology. 2025 Jun; 16: 1583421. doi: 10.3389/fimmu.2025.1583421.

[19] Beudeker BJ, Groothuismink ZM, van der Eijk AA, Debes JD, Boonstra A. Circulating Cytokines Reflect the Etiology-Specific Immune Environment in Cirrhosis and HCC. Cancers. 2022 Oct; 14(19): 4900. doi: 10.3390/cancers14194900.

[20] Ji F, Kang Q, Wang L, Liu L, Ke Y, Zhu Y *et al.* Prognostic Significance of the Neutrophil-to-Lymphocyte Ratio in Patients with Distal Cholangiocarcinoma. Medicine. 2020 Oct; 99(43): 22827. doi: 10.1097/MD.0000000000022827.

[21] Wang T and Zhang KH. New Blood Biomarkers for the Diagnosis of AFP-Negative Hepatocellular Carcinoma. Frontiers in Oncology. 2020 Aug; 10: 1316. doi: 10.3389/fonc.2020.01316.

[22] Chicco D and Oneto L. Computational Intelligence Identifies Alkaline Phosphatase, Alpha-Fetoprotein, and Hemoglobin Levels as Most Predictive Survival Factors for Hepatocellular Carcinoma. Health Informatics Journal. 2021 Jan; 27(1): 1-26. doi: 10.1177/1460458220984205.

[23] Ali S, Nazeer A, Tipu I. The Correlation Between Alpha-Fetoprotein and Liver Function Tests. BioScientific Review. 2019 Dec; 1(4): 10-19. doi: 10.32350/BSR.0104.02.

[24] Das SS, Hossain MS, Sultana A, Rana FA, Hossen A, Maowla MS *et al.* The Influence of Chronic Kidney Disease on Hepatocellular Carcinoma. Journal of Primeasia. 2025 Apr; 6(1): 1-8. doi: 10.25163/primeasia.6110204.

[25] Yap DY, Seto WK, Fung J, Chok SH, Chan SC, Chan GC *et al.* Serum and Urinary Biomarkers That Predict Hepatorenal Syndrome in Patients with Advanced Cirrhosis. Digestive and Liver Disease. 2017 Feb; 49(2): 202-206. doi: 10.1016/j.dld.2016.11.001.

[26] Blanco Abad C, Gomila Pons P, Campos Ramirez S, Álvarez Alejandro M, Torres Ramón MI, Miramar Gallart MD *et al.* Hereditary Pancreatic Cancer: Advances in Genetic Testing, Early Detection Strategies, and Personalized Management. Journal of Clinical Medicine. 2025 Jan; 14(2): 367. doi: 10.3390/jcm14020367.

[27] Munir M, Maqbool M, Ayyaz J, Anis S, Maqbool S. Correlation of Hepatocellular Carcinoma with Different Levels of Alpha-Fetoprotein in Pakistani Population. Annals of PIMS-Shaheed Zulfiqar Ali Bhutto Medical University. 2021 Nov; 17(3): 260-265. doi: 10.48036/apims.v17i3.565.