E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.481

Research Article

Predictive Role of Liver Functional Reserve, Serum Alpha-Fetoprotein, and Histopathological Grade in Patients Receiving Combination Immunotherapy for Advanced Hepatocellular Carcinoma

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Received: 09.06.2026, Revised: 10.08.2026, Accepted: 22.08.2026

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is frequently diagnosed at an advanced stage, when impaired hepatic reserve and aggressive tumor biology may adversely affect the efficacy of systemic immunotherapy. Liver functional reserve, serum alpha-fetoprotein (AFP), and histopathological grade may therefore provide important predictive information.

Objective: To determine the predictive role of liver functional reserve, serum AFP, and histopathological grade in patients with advanced HCC receiving combination immunotherapy.

Methods: A prospective observational study was conducted in a tertiary hospital among 100 patients with advanced HCC receiving combination immunotherapy. Baseline liver function was assessed using Child–Pugh classification and albumin-bilirubin (ALBI) grade. Serum AFP, bilirubin, albumin, ALT, AST, and other biochemical parameters were recorded. Histopathological tumor grade was determined according to tumor differentiation. Treatment response was assessed radiologically, while progression-free survival (PFS) and overall survival (OS) were evaluated during follow-up. Associations between baseline variables and treatment outcomes were analyzed using logistic regression and Cox proportional-hazards models.

Results: Among 100 patients, 38 (38.0%) achieved an objective response, including 12 (12.0%) complete and 26 (26.0%) partial responses, while 34 (34.0%) had stable disease and 28 (28.0%) showed progressive disease. Objective response was significantly higher in patients with Child–Pugh class A than class B (45.5% vs. 18.2%, p=0.008) and in patients with ALBI grade 1 compared with grades 2–3 (52.9% vs. 26.0%, p=0.006). Patients with AFP <400 ng/mL demonstrated a significantly higher response rate than those with AFP ≥400 ng/mL (46.8% vs. 22.2%, p=0.011). Poorly differentiated tumors were associated with a lower objective response compared with well/moderately differentiated tumors (20.0% vs. 43.8%, p=0.018). Median PFS was 8.7 months in Child–Pugh A patients compared with 4.6 months in Child–Pugh B patients (p=0.003), while median OS was 18.9 and 10.2 months, respectively (p<0.001). On multivariate analysis, impaired liver functional reserve (HR=2.18, 95% CI: 1.31–3.63, p=0.003), AFP ≥400 ng/mL (HR=1.91, 95% CI: 1.16–3.15, p=0.011), and poor histopathological differentiation (HR=1.84, 95% CI: 1.08–3.14, p=0.025) were independently associated with shorter OS.

Conclusion: Preserved liver functional reserve, lower serum AFP, and favorable histopathological grade were significantly associated with improved response and survival among patients with advanced HCC receiving combination immunotherapy. The combined assessment of hepatic reserve, AFP, and tumor differentiation may provide a useful approach for pretreatment risk stratification and prediction of immunotherapy outcomes.

Keywords: Liver Functional Reserve, serum AFP, histopathological grade, advanced HCC, combination immunotherapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the predominant primary malignancy of the liver and represents a major global health burden. HCC accounts for approximately 90% of primary liver cancers and commonly develops in the setting of chronic liver disease and cirrhosis. Despite advances in surveillance, diagnosis, and treatment, a substantial proportion of patients are diagnosed with advanced disease, for which systemic therapy remains the principal treatment strategy [1].

The therapeutic landscape of advanced HCC has changed considerably with the introduction of immune checkpoint inhibitor (ICI)-based combination therapies. Atezolizumab plus bevacizumab demonstrated significantly improved overall survival (OS) and progression-free survival (PFS) compared with sorafenib in the IMbrave150 trial, with updated median OS of 19.2 months versus 13.4 months, respectively [2]. Similarly, the combination of tremelimumab and durvalumab has provided an additional immunotherapeutic option for unresectable HCC, with evidence supporting the efficacy of dual immune checkpoint blockade targeting CTLA-4 and PD-L1 pathways [3]. Current clinical guidelines recognize atezolizumab plus bevacizumab and durvalumab plus tremelimumab as important first-line systemic treatment options for appropriately selected patients with advanced HCC [4].

An important characteristic distinguishing HCC from many other solid malignancies is the coexistence of tumor progression with variable degrees of underlying hepatic dysfunction. Consequently, treatment outcomes are influenced not only by tumor burden and malignant behavior but also by the functional reserve of the non-tumorous liver. The Barcelona Clinic Liver Cancer (BCLC) strategy emphasizes assessment of liver function, tumor burden, and performance status when determining prognosis and treatment allocation [5]. Child–Pugh classification remains widely used in clinical practice, while the albumin-bilirubin (ALBI) grade provides an objective assessment based on serum albumin and bilirubin concentrations.

Liver functional reserve may be particularly important in patients receiving immunotherapy because impaired hepatic function is independently associated with poorer clinical outcomes. A systematic review and meta-analysis involving 4,483 HCC patients treated with ICIs demonstrated that both Child–Pugh and ALBI scores were associated with survival. Patients with impaired liver function had significantly shorter OS and PFS, while ALBI grading provided relatively simple and reliable prognostic stratification [6]. These findings suggest that assessment of hepatic reserve should be considered an important component of pretreatment risk assessment in advanced HCC.

Serum alpha-fetoprotein (AFP) is another clinically important biomarker in HCC. Although AFP has limited sensitivity and specificity for diagnosis when used alone, elevated serum concentrations are frequently associated with increased tumor burden and aggressive tumor biology. Its prognostic relevance in patients receiving immunotherapy has been supported by several studies. A pooled analysis of 44 retrospective studies involving 5,322 patients found that elevated AFP was associated with shorter OS and PFS in patients receiving ICIs. Moreover, an early decline in AFP was associated with improved OS, PFS, objective response rate, and disease control rate [7].

The dynamic behavior of AFP may therefore provide additional information regarding treatment effectiveness. A systematic review and meta-analysis involving 26 studies and 3,056 HCC patients demonstrated that AFP reduction following targeted therapy or ICI treatment was associated with improved OS and PFS, whereas an increase in AFP was associated with substantially poorer outcomes [8]. These findings support AFP as a readily accessible biomarker that may complement radiological assessment and conventional clinical prognostic variables.

In addition to hepatic reserve and serum biomarkers, histopathological characteristics provide important information regarding the biological aggressiveness of HCC. Tumor differentiation reflects the extent to which malignant hepatocytes retain the structural and functional characteristics of normal hepatocytes. Poorly differentiated tumors generally exhibit more aggressive behavior and may be associated with vascular invasion, rapid progression, and unfavorable survival. Furthermore, recent prognostic models for ICI-

treated HCC have demonstrated that AFP, ALBI, Child–Pugh stage, BCLC stage, vascular invasion, tumor characteristics, and treatment-related factors can contribute to prediction of OS and PFS [9]. This supports a multidimensional approach in which host hepatic function and tumor biology are considered together.

Despite the expanding role of combination immunotherapy in advanced HCC, treatment response remains heterogeneous. Patients with similar tumor stages may experience markedly different therapeutic outcomes because of differences in hepatic functional reserve, tumor biomarker profile, and histopathological aggressiveness. Therefore, identifying readily available parameters capable of predicting treatment response and survival remains clinically important.

The present study was designed to evaluate the predictive role of liver functional reserve, serum AFP, and histopathological grade in patients with advanced HCC receiving combination immunotherapy. Specifically, the study aimed to determine the association of these parameters with objective treatment response, progression-free survival, and overall survival and to assess whether their combined evaluation could improve pretreatment prognostic stratification in this patient population.

MATERIALS AND METHODS

A retrospective observational study was conducted at a tertiary-care teaching hospital in Pakistan in the Department of Medical Oncology, after taking IRB permission. The study included adult patients aged ≥18 years with histologically or radiologically confirmed advanced or unresectable hepatocellular carcinoma (HCC) who received combination immunotherapy between January 2022 and December 2025. Patients with BCLC stage B or C disease who were not candidates for curative surgical or locoregional treatment were eligible. Patients were identified through hospital oncology and hepatology records, and demographic characteristics, clinical history, laboratory investigations, radiological findings, histopathological reports, treatment details, and follow-up information were retrieved from electronic medical records. Patients with another active malignancy, previous liver transplantation, previous systemic immunotherapy, incomplete baseline laboratory or clinical data, absence of evaluable post-treatment imaging, or inadequate follow-up were excluded.

Patients received combination immunotherapy according to institutional treatment protocols and the treating oncologist's clinical assessment. The principal treatment regimen consisted of intravenous atezolizumab 1200 mg combined with bevacizumab 15 mg/kg administered every 3 weeks. Treatment was continued until radiological disease progression, unacceptable toxicity, clinical deterioration, withdrawal of treatment, or death. Baseline clinical and laboratory data obtained within 14 days before initiation of immunotherapy were recorded. These included serum bilirubin, albumin, ALT, AST, alkaline phosphatase, GGT, prothrombin time/INR, serum creatinine, complete blood count, platelet count, and serum alpha-fetoprotein (AFP). AFP was measured using the hospital's standardized automated immunoassay system and expressed in ng/mL. For analysis, baseline AFP was categorized using 400 ng/mL as the principal cut-off.

Liver functional reserve was assessed using the Child–Pugh classification and albumin-bilirubin (ALBI) grade. The Child–Pugh score was calculated using serum bilirubin, serum albumin, prothrombin time/INR, ascites, and hepatic encephalopathy, and patients were categorized into Child–Pugh classes A, B, or C. The ALBI score was calculated using the formula: ALBI score = (log10 bilirubin × 0.66) + (albumin × −0.085), with bilirubin expressed in μmol/L and albumin in g/L. Patients were classified as ALBI grade 1 (≤−2.60), grade 2 (>−2.60 to ≤−1.39), or grade 3 (>−1.39). Histopathological reports were reviewed by consultant histopathologists, and tumors were categorized according to differentiation as well differentiated, moderately differentiated, or poorly differentiated. For statistical analysis, well- and moderately differentiated tumors were grouped together and compared with poorly differentiated tumors. Where available, additional pathological features including vascular invasion and tumor necrosis were also recorded.

Baseline tumor burden was evaluated using contrast-enhanced computed tomography or magnetic resonance imaging before initiation of treatment. Follow-up imaging was generally performed after 8–12 weeks of therapy and subsequently according to clinical requirements. Treatment response was assessed using modified Response Evaluation

Criteria in Solid Tumors (mRECIST) and categorized as complete response, partial response, stable disease, or progressive disease. Objective response rate was defined as complete or partial response, whereas disease control rate included complete response, partial response, and stable disease. The primary outcome was the association of baseline liver functional reserve, serum AFP, and histopathological grade with objective treatment response. Secondary outcomes included progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from initiation of immunotherapy to documented disease progression or death from any cause, while OS was defined as the time from treatment initiation to death from any cause or the last documented follow-up.

Statistical analysis was performed using IBM SPSS Statistics. Continuous variables were expressed as mean ± standard deviation or median with interquartile range according to data distribution, whereas categorical variables were presented as frequencies and percentages. Differences between categorical variables were evaluated using the chi-square or Fisher's exact test, while independent-samples t-test or Mann–Whitney U test was used for continuous variables according to distribution. Kaplan–Meier survival curves were generated for estimation of PFS and OS, and survival distributions were compared using the log-rank test. Cox proportional-hazards regression was performed to identify independent predictors of PFS and OS, and hazard ratios with 95% confidence intervals were calculated. Multivariable logistic regression was used to determine independent predictors of objective treatment response. Receiver operating characteristic curve analysis was performed where appropriate to evaluate the discriminatory ability of AFP and liver functional parameters. A two-sided p-value <0.05 was considered statistically significant.

The study protocol was submitted to the institutional ethics committee of the participating tertiary-care hospital for approval. As this was a retrospective study based on routinely collected clinical data, a waiver of individual informed consent was sought in accordance with institutional policy. Patient confidentiality was maintained throughout the study, and all identifying information was removed from the analytical dataset. The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable ethical requirements.

RESULTS

A total of 100 patients with advanced hepatocellular carcinoma (HCC) receiving combination immunotherapy were included in the final analysis. The mean age of the study population was 61.8 ± 9.7 years, with a predominance of male patients (72.0%). Most patients had BCLC stage C disease (68.0%), while 32.0% had stage B disease. Child–Pugh class A was observed in 77 patients (77.0%), whereas 23 patients (23.0%) had class B disease. According to ALBI grading, 51 patients (51.0%) were classified as grade 1, 45 (45.0%) as grade 2, and 4 (4.0%) as grade 3. The median baseline AFP concentration was 386 ng/mL (IQR: 92–1,840), with 45 patients (45.0%) having AFP <400 ng/mL and 55 (55.0%) having AFP ≥400 ng/mL. Histopathological examination showed well-differentiated tumors in 12 patients (12.0%), moderately differentiated tumors in 52 (52.0%), and poorly differentiated tumors in 36 (36.0%).

Treatment Response

Following combination immunotherapy, 12 patients (12.0%) achieved complete response, 26 (26.0%) achieved partial response, 34 (34.0%) had stable disease, and 28 (28.0%) demonstrated progressive disease. The overall objective response rate was therefore 38.0%, while the disease control rate was 72.0%.

Treatment response was significantly associated with baseline hepatic functional reserve. Objective response was observed in 45.5% of patients with Child–Pugh class A compared with 18.2% of patients with Child–Pugh class B disease ($p=0.008$). Similarly, patients with ALBI grade 1 demonstrated a significantly higher objective response rate than those with ALBI grades 2–3 (52.9% vs. 26.0%, $p=0.006$).

Patients with AFP <400 ng/mL had a significantly greater objective response than those with AFP ≥400 ng/mL (46.8% vs. 22.2%, $p=0.011$). Tumor differentiation was also significantly associated with treatment response. Patients with well/moderately differentiated tumors had an objective response rate of 43.8%, compared with 20.0% among patients with poorly differentiated tumors ($p=0.018$).

Table 1. Baseline Clinical, Biochemical and Histopathological Characteristics of Study Participants

Variable	Total (n=100)
Age, years, mean ± SD	61.8 ± 9.7
Male sex, n (%)	72 (72.0)
Female sex, n (%)	28 (28.0)
BCLC stage B, n (%)	32 (32.0)
BCLC stage C, n (%)	68 (68.0)
Child–Pugh A, n (%)	77 (77.0)
Child–Pugh B, n (%)	23 (23.0)
ALBI grade 1, n (%)	51 (51.0)
ALBI grade 2, n (%)	45 (45.0)
ALBI grade 3, n (%)	4 (4.0)
AFP, median (IQR), ng/mL	386 (92–1,840)
AFP <400 ng/mL, n (%)	45 (45.0)
AFP ≥400 ng/mL, n (%)	55 (55.0)
Well differentiated, n (%)	12 (12.0)
Moderately differentiated, n (%)	52 (52.0)
Poorly differentiated, n (%)	36 (36.0)

Table 2. Association of Liver Functional Reserve, AFP and Histopathological Grade with Treatment Response

Variable	Objective Response n (%)	No Objective Response n (%)	p-value
Child–Pugh A	35 (45.5)	42 (54.5)	
Child–Pugh B	3 (18.2)	20 (81.8)	0.008
ALBI grade 1	27 (52.9)	24 (47.1)	
ALBI grades 2–3	11 (22.4)	38 (77.6)	0.006
AFP <400 ng/mL	21 (46.7)	24 (53.3)	
AFP ≥400 ng/mL	17 (30.9)	38 (69.1)	0.011
Well/moderately differentiated	28 (43.8)	36 (56.2)	
Poorly differentiated	10 (27.8)	26 (72.2)	0.018

Survival Outcomes

During follow-up, 57 patients experienced disease progression and 49 patients died. The median progression-free survival for the overall cohort was 7.4 months. Patients with Child–Pugh class A disease had significantly longer PFS than those with Child–Pugh class B disease (8.7 vs. 4.6 months, log-rank p=0.003). Median PFS was also significantly longer among patients with ALBI grade 1 compared with grades 2–3 (10.1 vs. 5.6 months, p=0.002).

Patients with AFP <400 ng/mL had a median PFS of 9.1 months compared with 6.0 months among those with AFP ≥400 ng/mL (p=0.009). Similarly, patients with well/moderately differentiated tumors demonstrated longer PFS than those with poorly differentiated tumors (8.6 vs. 5.3 months, p=0.014).

The median overall survival of the study population was 16.4 months. Median OS was significantly longer in Child–Pugh class A patient than in Child–Pugh class B patients (18.9 vs. 10.2 months, p<0.001). Patients with ALBI grade 1 had a median OS of 21.3 months compared with 12.4 months among patients with ALBI grades 2–3 (p<0.001). Median OS was 19.8 months in patients with AFP <400 ng/mL compared with 13.1 months in those with AFP ≥400 ng/mL (p=0.006). Patients with well/moderately differentiated tumors also had better survival than those with poorly differentiated tumors (18.7 vs. 11.9 months, p=0.012).

Table 3. Progression-Free and Overall Survival According to Major Predictive Variables

Variable	Median PFS (months)	p-value	Median OS (months)	p-value
Child–Pugh A	8.7		18.9	

Child–Pugh B	4.6	**0.003**	10.2	**<0.001**
ALBI grade 1	10.1		21.3	
ALBI grades 2–3	5.6	**0.002**	12.4	**<0.001**
AFP <400 ng/mL	9.1		19.8	
AFP ≥400 ng/mL	6.0	**0.009**	13.1	**0.006**
Well/moderately differentiated	8.6		18.7	
Poorly differentiated	5.3	**0.014**	11.9	**0.012**

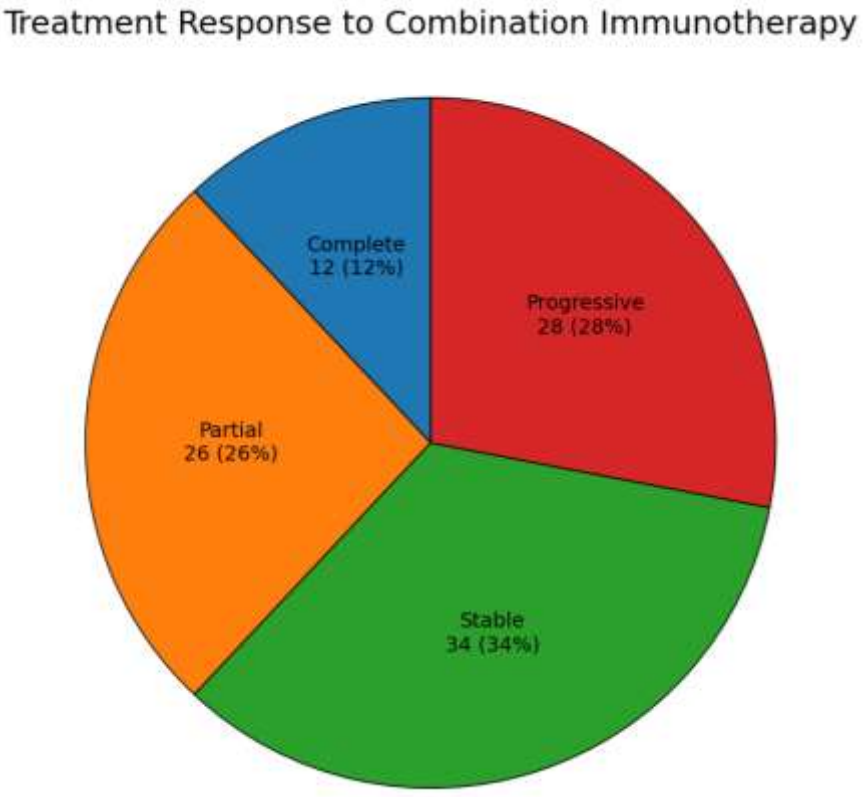
Multivariable Analysis

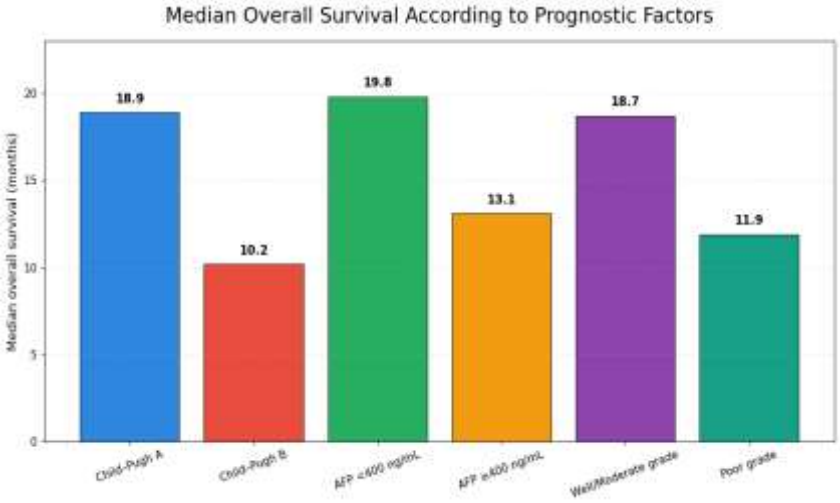
On multivariable Cox regression analysis, impaired liver functional reserve, elevated AFP, and poor histopathological differentiation remained independent predictors of inferior overall survival. Child–Pugh class B was associated with more than two-fold increased mortality risk compared with class A (HR=2.18, 95% CI: 1.31–3.63; p=0.003). AFP ≥400 ng/mL was independently associated with poorer OS (HR=1.91, 95% CI: 1.16–3.15; p=0.011), while poorly differentiated tumors were associated with increased mortality risk (HR=1.84, 95% CI: 1.08–3.14; p=0.025).

Table 4. Multivariable Cox Regression Analysis of Predictors of Overall Survival

Predictor	Hazard Ratio	95% CI	p-value
Child–Pugh B vs. A	2.18	1.31–3.63	**0.003**
AFP ≥400 vs. <400 ng/mL	1.91	1.16–3.15	**0.011**
Poor vs. well/moderately differentiated	1.84	1.08–3.14	**0.025**
BCLC stage C vs. B	1.67	1.04–2.68	**0.034**
Age ≥65 years	1.21	0.78–1.89	0.394

Overall, the findings demonstrated that preserved liver functional reserve, lower baseline AFP concentration, and favorable histopathological differentiation were significantly associated with improved treatment response and prolonged survival in patients receiving combination immunotherapy for advanced HCC.





DISCUSSION

The present study evaluated the predictive and prognostic significance of liver functional reserve, serum alpha-fetoprotein (AFP), and histopathological grade in patients with advanced hepatocellular carcinoma (HCC) receiving combination immunotherapy. The principal findings were that preserved hepatic functional reserve, lower baseline AFP concentration, and favorable tumor differentiation were significantly associated with better treatment response and prolonged survival. In the present cohort, patients with Child–Pugh class A disease demonstrated a significantly higher objective response rate than those with Child–Pugh class B disease, while ALBI grade 1 was associated with both greater treatment response and longer survival. Similarly, patients with AFP <400 ng/mL and those with well or moderately differentiated tumors experienced more favorable outcomes. These findings support the concept that outcome in advanced HCC is determined by an interaction between host liver function and tumor biological characteristics rather than tumor stage alone.

The association between hepatic functional reserve and treatment outcome observed in this study is consistent with previous evidence. A systematic review and meta-analysis of 41 studies involving 4,483 patients treated with immune checkpoint inhibitors demonstrated that both Child–Pugh and ALBI scores were significant predictors of overall and progression-free survival, with poorer liver function being associated with inferior outcomes [6]. The authors also suggested that ALBI may provide more objective and reproducible prognostic stratification than Child–Pugh classification. Our findings are concordant with this observation, as patients with ALBI grade 1 had substantially longer median overall survival than those with ALBI grades 2–3.

Real-world studies of atezolizumab plus bevacizumab have further emphasized the importance of hepatic reserve. D'Alessio et al. reported outcomes from 216 patients treated across 11 tertiary centers and found that patients with Child–Pugh B disease had poorer outcomes than those with Child–Pugh A liver function [10]. Similarly, Hiraoka et al. demonstrated that hepatic function could change during atezolizumab plus bevacizumab therapy and that ALBI was a useful measure for monitoring hepatic reserve during treatment [11]. These observations are clinically relevant because advanced HCC frequently develops in a cirrhotic liver, and deterioration of hepatic function may limit the ability of patients to tolerate systemic treatment even when tumor-directed therapy remains potentially effective.

Our findings regarding Child–Pugh class are also consistent with a large multicenter real-world study specifically examining atezolizumab plus bevacizumab in patients with impaired liver function. Ohama et al. reported significantly poorer outcomes among Child–Pugh B patients compared with Child–Pugh A patients, supporting the prognostic importance of hepatic reserve in routine clinical practice [12]. More recently, a multicenter cohort of 322 patients receiving first-line atezolizumab plus bevacizumab demonstrated a median overall survival of 21.6 months in Child–Pugh A patients compared with 9.1 months in Child–Pugh B7 and 4.7 months in patients with Child–Pugh B8–C12 disease. ALBI grade also significantly stratified survival among patients with Child–Pugh A disease [13]. The

consistency of these findings with our results strengthens the evidence that liver functional reserve should be considered an important pretreatment prognostic variable.

In the present study, baseline AFP ≥400 ng/mL was significantly associated with a lower objective response rate and shorter PFS and OS. This observation is supported by a pooled analysis of 44 retrospective studies involving 5,322 patients treated with immune checkpoint inhibitors. High AFP was associated with shorter OS and PFS, while early AFP response was associated with improved survival and higher disease-control rates [7]. Similarly, a meta-analysis specifically evaluating early AFP response demonstrated that reduction in AFP following systemic treatment was associated with improved survival outcomes [8]. These findings indicate that AFP may provide information about tumor biological aggressiveness in addition to its conventional role as a tumor marker.

The prognostic relevance of AFP appears to extend beyond a single baseline measurement. Tanaka et al., in a multicenter retrospective study of 371 patients receiving atezolizumab plus bevacizumab, demonstrated that a composite tumor-marker score incorporating AFP, AFP-L3, and des-gamma-carboxy prothrombin could significantly stratify both overall and progression-free survival [14]. More recently, Yang et al. evaluated 536 patients receiving bevacizumab plus immunotherapy and demonstrated that dynamic AFP trajectories were independently associated with PFS and OS. Patients demonstrating a rapid decline in AFP after treatment had substantially more favorable outcomes than those with persistently elevated or increasing AFP concentrations [15]. Therefore, the baseline AFP findings in our study may represent only one component of a broader role for longitudinal AFP monitoring during immunotherapy.

Histopathological differentiation was also significantly associated with treatment response and survival in the present study. Patients with well or moderately differentiated tumors demonstrated a higher objective response rate and longer median PFS and OS than patients with poorly differentiated tumors. Tumor differentiation is an established marker of biological aggressiveness and may reflect differences in vascular invasion, proliferative activity, tumor architecture, and molecular characteristics. Although histological grade is not routinely available in every patient with HCC diagnosed radiologically, its availability in biopsy-confirmed cases may provide additional prognostic information.

The relationship between histopathological characteristics and prognosis is particularly relevant in the era of immunotherapy because HCC is biologically heterogeneous. Certain histological patterns are associated with distinct molecular and immune characteristics. For example, the macrotrabecular-massive subtype has been associated with aggressive tumor behavior, vascular invasion, high AFP levels, and unfavorable prognosis [16]. Such biological heterogeneity may partly explain why patients with apparently similar clinical stages can demonstrate markedly different responses to immune-based treatment.

An important finding of the present study was that the three principal variables—hepatic functional reserve, AFP concentration, and histopathological grade—provided complementary prognostic information. Liver functional reserve primarily reflects the condition of the non-tumorous liver, whereas AFP provides information related to tumor burden and biological activity, and histopathological grade reflects tumor differentiation and aggressiveness. Their simultaneous evaluation may therefore provide a more comprehensive assessment than any individual parameter alone. This concept is supported by a systematic review and meta-analysis of 47 cohorts involving 7,649 ICI-treated HCC patients, in which AFP, ALBI, Child–Pugh stage, BCLC stage, vascular invasion, and other clinical variables were identified as predictors of survival [9].

The overall objective response rate of 38.0% observed in our cohort was encouraging and indicates clinically meaningful activity of combination immunotherapy. However, the presence of progressive disease in 28.0% of patients emphasizes the heterogeneity of treatment benefit. Real-world studies have generally reported somewhat lower response rates than pivotal clinical trials, partly because routine clinical populations include patients with poorer hepatic reserve, greater tumor burden, and comorbidities that are often underrepresented in randomized trials [10,13]. Thus, the identification of readily available pretreatment markers remains important for patient selection and prognostic counselling.

The survival findings further emphasize the importance of hepatic reserve. Median OS was

18.9 months in Child–Pugh A patients compared with 10.2 months in Child–Pugh B patients. The multivariable analysis demonstrated that Child–Pugh B status remained independently associated with increased mortality after adjustment for AFP, tumor differentiation, and BCLC stage. This suggests that hepatic dysfunction is not merely a surrogate for tumor severity but represents an independent determinant of clinical outcome. Similar findings have been reported in real-world cohorts in which Child–Pugh and ALBI classifications remained independently associated with survival after adjustment for tumor-related variables [13].

The multivariable analysis also demonstrated that AFP ≥400 ng/mL and poor histopathological differentiation were independently associated with shorter overall survival. These findings suggest that the prognostic value of AFP and tumor grade persists even after accounting for hepatic functional reserve. Consequently, a patient with preserved liver function may still have an unfavorable prognosis if characterized by markedly elevated AFP and poorly differentiated disease. Conversely, patients with preserved hepatic function, lower AFP, and favorable differentiation may represent a subgroup with a greater probability of benefiting from combination immunotherapy.

From a clinical perspective, the findings suggest that pretreatment assessment of advanced HCC should not rely exclusively on radiological tumor stage. A practical prognostic framework incorporating Child–Pugh or ALBI grade, serum AFP, and histopathological differentiation may improve baseline risk stratification. ALBI is particularly attractive because it is objective, inexpensive, and calculated from routinely available serum albumin and bilirubin values [6,13]. AFP is similarly accessible in most tertiary-care settings, including resource-constrained environments, making this combination potentially useful in Pakistani clinical practice.

LIMITATIONS

The present study has several limitations. First, its retrospective design introduces the possibility of selection bias and incomplete documentation. Second, the study was conducted at a single tertiary-care hospital, which may limit generalizability to other Pakistani institutions. Third, histopathological grading was not available for every patient, potentially introducing selection bias in analyses involving tumor differentiation. Fourth, the sample size was relatively modest, and the study lacked an independent external validation cohort. Finally, other potentially important biomarkers, including neutrophil-to-lymphocyte ratio, PIVKA-II, AFP-L3, immune-cell profiles, and genomic characteristics, were not incorporated into the present analysis.

Despite these limitations, the study provides clinically relevant evidence that liver functional reserve, AFP, and histopathological grade can independently and collectively contribute to prediction of treatment response and survival in advanced HCC receiving combination immunotherapy. The findings are consistent with accumulating real-world evidence and support further prospective multicenter studies in Pakistani populations. Future studies should evaluate dynamic changes in ALBI and AFP during treatment and develop validated composite prediction models incorporating hepatic function, tumor biomarkers, histopathology, and immune-related parameters.

CONCLUSION

In conclusion, preserved hepatic functional reserve, lower serum AFP concentration, and favorable histopathological differentiation were associated with improved treatment response and survival in patients with advanced HCC receiving combination immunotherapy. These readily accessible parameters may provide a practical framework for pretreatment risk stratification and prognostic counselling, particularly in tertiary-care settings where individualized treatment selection is increasingly important.

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