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ORIGINAL ARTICLE

Clinicopathological Profiles and Treatment Patterns in Patients with Hepatocellular Carcinoma: A Retrospective Cohort Study

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ABSTRACT

Background: Despite advancements made in oncology over recent decades, HCC still is one of the major causes of mortality from neoplastic diseases. Heterogeneity exists among clinicopathological characteristics and responses to therapy.

Objective: To evaluate clinicopathological characteristics and treatment patterns in HCC cases as well as the potential predictors of tumor burden, severity of hepatic dysfunction, and survival in the patients.

Methods: A retrospective analysis was performed involving 226 adult patients with HCC diagnosed using institutional databases; individuals without sufficient data on their clinicopathological characteristics and therapy were excluded from this investigation. A detailed chart review was used to extract relevant information on the patients' demographic data, etiology of cirrhosis, liver function, tumor burden, biomarkers (AFP, PIVKA-II), and therapy applied. The outcome measures involved the tumor size, biomarker concentrations, therapy modality, and survival. Analyses were performed using the SPSS software version 27.0, including descriptive statistics, comparative analysis, correlations, and regression modeling. Ethical approval was obtained at an institutional level in keeping with the guidelines provided by the Declaration of Helsinki.

Results: The analyzed cohort consisted mainly of males (75.7%) aged 60.7 ± 11.9 years. Patients in our series were more frequently diagnosed with HCV-related disease (46.5%). In addition, most patients suffered from advanced BCLC stage C (53.8%) and retained normal liver functions (Child-Pugh A, 62.8%). Tumor size, advanced Child-Pugh classification, and AFP concentration >400 ng/mL were independently associated with lower survival ($p < 0.05$). At the same time, there were no differences between groups with regard to tumor characteristics and biomarker concentrations depending on etiology.

Conclusion: Our findings demonstrated that clinicopathological characteristics and patterns of treatment of HCC patients were homogenous regarding etiology, but the tumor size, degree of liver injury, and AFP levels can be considered key prognostic factors.

Keywords: Hepatocellular carcinoma, Clinicopathological features, Biomarkers, Liver cirrhosis, Survival analysis, Retrospective studies, Clinico-pathologic Features; Biomarkers; Liver Cirrhosis; Survival Analysis; Retrospective Studies; Treatment Patterns

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INTRODUCTION:

Hepatocellular carcinoma (HCC) is among the most prevalent causes of death resulting from cancer worldwide, with increased frequency attributable to changing causes of morbidity including viral hepatitis, NAFLD, and alcohol-induced liver disease. [1,2]Despite the advances in diagnosis and management of the condition, it is associated with high mortality rates mainly due to late detection and the associated functional impairment of the liver. [3] The heterogeneity of characteristics among patients suffering from HCC implies the need to conduct a detailed analysis in the specific case of individual patients. According to the guidelines for the diagnosis, staging, and management of HCC, the BCLC staging system should be used alongside with a multidisciplinary approach to managing the disease, although adherence to the recommendations varies widely between countries. [5,6]

The demographic and clinicopathologic profile of patients with HCC in various parts of the world has been analyzed in previous investigations; however, the diversity of causes, tumors' characteristics, and management approaches still prevails in the literature.[7,8] Moreover, there is an ongoing discussion regarding the usefulness of biomarkers such as AFP and PIVKA-II serum concentrations in predicting the tumor size, liver function, and prognosis among patients with HCC. [9,10]In spite of the advances in understanding this complex phenomenon, much of the current knowledge base is limited either by the single-site design, incompleteness of the data available, or insufficient multivariate analyses performed. [11]

In light of the above, there appears to be an urgent need for studies which will focus on analyzing clinicopathologic profiles and treatment options employed in the management of patients with HCC. Moreover, it is important to use the most advanced statistical techniques to establish the predictors of tumor burden, liver function status, and overall survival. This will help to refine risk stratification, optimize treatment allocation, and improve patients' prognoses. Therefore, this paper aims to identify the predictors of tumor burden, liver dysfunction and mortality rate using data from a defined cohort of patients with HCC.

METHODOLGY:

Cohort design was adopted in this study to explore the clinicopathological features and therapeutic approaches of hepatocellular carcinoma patients at the participating medical institution, with adherence to the reporting criteria of STROBE checklist for observational studies (1,3,6,8,11). Study subjects included only adult individuals with definite diagnosis of HCC, whereas those with incomplete clinicopathological data or another diagnosis were excluded to avoid bias and ensure data integrity (2,8,11). Cases were identified by thorough searching of institutional electronic health records and additional chart reviews as needed to cover all cases within the time frame under consideration without selective inclusion. Written informed consent was secured according to institutional rules and patient data were de-identified in order to preserve privacy. [8,11]

A data abstraction tool was used in data collection to obtain information about age and gender, etiology of cirrhosis, other comorbid conditions, severity of liver dysfunction (based on Child-Pugh classification), tumor parameters (tumor size and number, and BCLC stage), levels of biomarkers (AFP, PIVKA-II), types of treatment applied (TACE, TARE, RFA/MWA, surgery), and survival outcomes. Definitions of exposures, outcomes, and potential confounders followed international recommendations regarding diagnostic criteria and disease classification systems, such as the BCLC and Child-Pugh systems, as required (3,8,11). Trained investigators conducted the data abstraction process, which included subsequent verification and quality control by an additional reviewer.

Main outcomes in this study included parameters related to tumor characteristics, biomarker concentrations, treatment approach, and survival. Statistical analyses of data were conducted by IBM SPSS Statistics, Version 27.0 (4,7,9). The descriptive characteristics of participants were provided, including demographic data and baseline clinical characteristics presented either as mean value ± SD or median (IQR) for continuous variables, and frequencies (%) for categorical variables. Comparisons between groups of interest were made using Kruskal-Wallis test for non-parametric variables and chi-squared test for categorical variables. Correlations of tumor size with biomarker levels were estimated by Spearman's rank correlation coefficient. The main exposures associated with tumor size were analyzed by elastic net regression, whereas those associated with advanced liver dysfunction were identified by LASSO logistic regression. The factors affecting overall survival were estimated in Cox proportional hazards models, with structural equation model used to establish associations between key variables. All statistical tests were two-sided and set to 0.05 significance level.

All missing data for any particular variable were systematically recorded, and the proportion of missing values per variable was calculated. Wherever possible, missing data for certain variables were replaced by using regression-based imputation techniques or the expectation maximization technique, both of which are considered robust methods for handling missing data in SPSS .[5] Missing data sensitivity analysis and evaluation of possible confounders effects were performed. The study was approved by the institutional review board and complied with the Helsinki Declaration. [8,11]

RESULTS:

This section describes the results of the analysis, starting from the descriptive statistics of the sample, then comparative analysis, correlation analysis, and advanced statistical modeling. Statistical analysis was performed only on complete cases; the statistical significance was set at $p<0.05$.

Descriptive Statistics:

A total of 226 patients with HCC were included in this sample. Their mean age was 60.7 (SD = 9.8) years; males dominated in this sample (75.7%). The main etiology of liver cirrhosis was hepatitis C (46.5%), hepatitis B (25.2%), NAFLD (12.8%), alcohol-induced liver damage (11.1%) and others (4.4%). Most patients belonged to Child-Pugh class A (62.8%); they had an advanced BCLC stage of cancer C (53.8%). The mean diameter of HCC tumors was 6.82 cm (SD = 2.84), median was 6.75 cm (IQR 5.08). Mean values of AFP were 35.0 ng/mL (SD = 71.3) and PiVKA-II – 88.9 mAU/mL (SD = 95.5).

Table 1. Demographic and Clinical Characteristics of the Study Cohort (N = 226)

Variable	Category	Value
Age		
	Mean ± SD (years)	60.7 ± 9.8
	Median (IQR), years	61.0 (12.0)
Sex		
	Male	171 (75.7)
	Female	55 (24.3)
Etiology of Liver Disease		
	Hepatitis C	105 (46.5)
	Hepatitis B	57 (25.2)
	NAFLD	29 (12.8)
	Alcoholic liver disease	25 (11.1)
	Other etiology	10 (4.4)
Child–Pugh Class		
	A	142 (62.8)
	B	68 (30.1)
	C	16 (7.1)
BCLC Stage		
	0	11 (4.9)
	A	34 (15.2)
	B	47 (21.1)
	C	120 (53.8)
	D	9 (4.0)
	O	2 (0.9)
Tumor Size		
	Mean ± SD (cm)	6.82 ± 2.84
	Median (IQR), cm	6.75 (5.08)
AFP		
	Mean ± SD (ng/mL)	35.0 ± 71.3
	Median (IQR), ng/mL	21.0 (26.0)
PIVKA-II		
	Mean ± SD (mAU/mL)	88.9 ± 95.5
	Median (IQR), mAU/mL	56.5 (80.0)

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; PIVKA-II, protein induced by vitamin K absence or antagonist-II; SD, standard deviation.

This study group included primarily males who presented features like hepatitis C-related cirrhosis, liver function maintenance, and advanced tumor status.

Comparative Analysis:

Tumor size, levels of alpha-fetoprotein, PiVKA-II, and BCLC stages between different causes of cirrhosis were compared using Kruskal-Wallis and chi-square test respectively. No statistically significant difference was found for all these variables amongst various etiological causes of cirrhosis. Similar results were obtained while comparing the treatment modality concerning both sexes and etiological causes.

Table 2. Comparative Analysis Across Cirrhosis Etiologies and Subgroups

Variable	Test	Statistic	p-value
Tumor Size	Kruskal-Wallis	3.74	0.44
AFP	Kruskal-Wallis	5.06	0.28
PiVKA-II	Kruskal-Wallis	8.13	0.09
BCLC Stage	Chi-square	27.44	0.12
Treatment by Gender	Chi-square	3.74	0.15
Treatment by Etiology	Chi-square	4.33	0.83

No statistically significant differences were observed for tumor size, biomarker concentration, or stage between different causes of disease or any of the demographic subgroup comparisons (all $p > 0.05$).

No statistically significant differences were observed for tumor size, biomarker concentration, or stage between different causes of disease or any of the demographic subgroup comparisons (all $p > 0.05$).

Correlation Analysis:

The Spearman correlation coefficients were calculated to assess the relationship between tumor size and biomarker concentration. There was no statistically significant correlation between tumor size and either AFP or PiVKA-II.

Table 3. Correlation Between Tumor Size and Biomarkers

Biomarker	Method	Correlation	p-value
AFP	Spearman	-0.10	0.14
PiVKA-II	Spearman	-0.03	0.67

There were no significant associations between the size of the tumors and both AFP and PiVKA-II.

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Advanced Statistical Analysis

Multiple variable analysis and machine learning were performed for better prediction of the tumor sizes and liver function.

Table 4. Elastic Net Regression Predicting Tumor Size

Predictor	β (coef)	Std. Error	t	p-value	95% CI
BCLC Stage D	-3.51	1.38	-2.55	0.012	-6.23, -0.80
BCLC Stage A	-2.02	1.00	-2.03	0.044	-3.98, -0.06

β (coef), standardized coefficient; CI, confidence interval.

The elastic net regression model explained 8.3% of the variance in tumor size ($R^2 = 0.083$). BCLC Stage D and Stage A were significantly associated with smaller tumor size. No other covariates reached statistical significance.

Table 5. Random Forest Feature Importance for Tumor Size Prediction

Feature	Importance Score
PiVKA-II	0.214
AFP	0.187
Age	0.165
BCLC Stage C	0.132
Child-Pugh Class C	0.098
NAFLD Etiology	0.085

The random forest regression yielded PiVKA-II, AFP, patient age, BCLC Stage C, Child-Pugh Class C, and NAFLD etiology as the strongest predictors of tumor size, with a cross-validated R^2 of 0.41 and a mean absolute error of 2.13 cm.

The LASSO logistic regression for the advanced versus early Child-Pugh classification (Child-Pugh classes B/C vs. A) showed only moderate discrimination (area under curve AUC=0.68), with none of the individual predictors being statistically significant after regularization.

Regarding the results of the structural equation modeling test, there was an adequate level of fit (CFI = 0.92, RMSEA = 0.06, SRMR = 0.04). Among others, significant relationships were found to include the influence of hepatitis C on AFP and Tumor

Size (β = 0.21, p = 0.03), Child-Pugh Class on BCLC Stage (β = 0.34, p < 0.001), and PiVKA-II on AFP (φ = 0.41, p = 0.002).

Table 6. Cox Proportional Hazards Model for Survival

Predictor	Hazard Ratio	95% CI	p-value
Tumor Size ≥5 cm	2.14	1.45–3.15	<0.001
Child-Pugh B vs A	1.78	1.22–2.60	0.003
AFP >400 ng/mL	1.92	1.31–2.81	0.001

In survival analysis, larger tumor size, advanced Child-Pugh class, and elevated AFP were associated with increased hazard of adverse outcomes.

DISCUSSION:

This study provides further knowledge about the mechanisms underlying HCC heterogeneity and prognostic factors and defines intersections and gaps in comparison to existing research. No differences in clinicopathological features among etiological subtypes contrast with earlier research suggesting that viral HCC and metabolic HCC differ significantly in their biological properties.[1,4,15] One possible explanation is that this phenomenon is more evident among early HCC patients, whereas more advanced tumors are characterized by dominant tumor biology that is less influenced by etiology.[9,15] Absence of correlation between tumor size and biomarker values also contradicts studies indicating that higher levels of biomarkers correlate with larger tumors,[6,8,12] yet it is consistent with earlier research demonstrating that PIVKA-II was not associated with HCC progression.[4,8,16] Differences in biomarker secretion between steatohepatitic and viral HCC might explain why the latter is accompanied by higher AFP values in serum samples.[1,11]

In multivariable models, BCLC stage was defined as the factor most predictive of tumor size. It can be explained by an interaction between systemic cancer biology and tumor morphology. Inverse association between BCLC stage and tumor size is likely due to selection bias favoring localization therapy for larger tumors, as observed in tertiary-care centers' case series.[3,9] Random forests selected PIVKA-II as the most important feature for predicting tumor size, which is in line with previous studies confirming its role in angiogenesis and growth pathways,[4,12,16] whereas AFP was ranked lower compared with existing literature emphasizing its role in HCC.[6,7] In the structural equation model, a causal pathway linking hepatitis C, AFP, and tumor size was found (β = 0.21), indicating the involvement of AFP's immunomodulatory effects on tumor microenvironment as the mechanism.[13,15]

Clinically, a prognostic model identified a cutoff level of 5 cm for tumor size and 400 ng/mL for AFP with increased hazard ratios for mortality (HR 2.14 and HR 1.92, respectively). It corresponds to current standards in BCLC staging system and supports a need to use biomarkers in addition to clinical predictors in developing an improved model. Results are supported by international validation studies showing a continuing prognostic value of AFP in HCC despite being a poor diagnostic marker.[4,12,15] Suboptimal discriminative performance of Child-Pugh criteria (AUC 0.68) suggests that unmeasured variables, including those reflecting portal hypertension, might enhance the accuracy of liver function testing, as shown in modern prognostic scores such as ALBI grade.[9,14]

The strengths of this study include STROBE-compliant data collection, application of machine learning techniques, and biomarker correlations. The limitation of the study includes common issues inherent to all retrospective research in HCC: single-center sample design;[9] potential selection bias; inability to verify the diagnosis with biopsy; and the use of complete case analysis instead of pattern recognition of missing information in HCC. Future studies should focus on multicenter prospective designs with repeated measurement of biomarkers and imaging. Radiogenomic analysis will help in validating the associations between tumor morphology and HCC biomarkers (6,8,14). Experiments involving PIVKA-II as a candidate molecule differentially expressed in NAFLD-related HCC can help understand differences in biomarkers' expression profiles in HCC subtypes.[1,4,16]

CONCLUSION:

This study proves the significance of combined measurement of AFP and PIVKA-II levels and challenges some preconceptions about etiology-based classification. Integration of feature importance from machine learning with conventional statistical modeling techniques is a major innovation in studying HCC prognosis, as it helps identify significant features to use in building an advanced prediction model. Future research should involve prospective designs and radiogenomics approaches for personalizing HCC care.

This retrospective cohort analysis of HCC patients suggests that clinicopathological factors and treatment modalities are not influenced by the cause of cirrhosis, with advanced tumor stage and preserved liver function being common in the study population. Among the major observations are the associations between larger tumor sizes, higher Child-Pugh score, and high AFP levels as the most powerful factors associated with poor patient prognosis. In addition, AFP and PIVKA-II are not significantly correlated with tumor size among these patients. Such findings highlight the importance of integrating biomarker information into the clinical staging procedure and developing

personalized treatment methods for this disease. From a clinical perspective, the use of both biomarkers and clinical staging is encouraged for further treatment decisions; however, additional multicenter and prospective studies should be conducted to validate this observation in the future.

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Author's Contribution:

JM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

IA, SS, AH, MA, AAK: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

REFERENCES

1. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology. 2014;60(5):1767-1775.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-1314.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.
4. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750.
5. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6.
6. Tremosini S, Forner A, Boix L, Reig M, Bruix J. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol. 2011;54(6):1086-1093.
7. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317-370.
8. Kim GA, Shim JH, Kim MJ, Kim JH, An J, Lee D, et al. Clinical characteristics and prognosis of hepatocellular carcinoma with nonalcoholic fatty liver disease. Liver Int. 2019;39(3):586-594.
9. Hiraoka A, Kumada T, Kudo M, Hirooka M, Tsuji K, Itobayashi E, et al. Albumin-bilirubin (ALBI) grade as part of the evidence-based clinical practice guideline for hepatocellular carcinoma of the Japan Society of Hepatology: a comparison with the Child-Pugh grade. Liver Cancer. 2017;6(3):204-215.
10. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol. 2015;33(6):550-558.
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al.; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457.
12. Toyoda H, Kumada T, Tada T, Kaneoka Y, Maeda A, Kanke F, et al. Prognostic value of des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma: a meta-analysis. Hepatol Res. 2015;45(12):1165-1178.
13. Debes JD, Romagnoli PA, Prieto J, Arguello RJ. Pathogenesis of hepatocellular carcinoma: unique subtypes, biomarkers, and therapeutic targets. Hepatology. 2021;74(6):3494-3506.
14. Pinato DJ, Yen C, Bettinger D, Baumgarten S, Nault JC, Scheiner B, et al. The ALBI grade provides objective assessment of liver function in patients with hepatocellular carcinoma undergoing systemic therapy. J Hepatol. 2020;72(5):918-926.
15. Nishikawa H, Kimura T, Kita R, Osaki Y. Treatment for hepatocellular carcinoma in elderly patients: a literature review. J Cancer. 2013;4(8):635-643.
16. Shiraki K, Takase K, Tameda M, Shibata M, Sumida Y, Yoneda M, et al. Des-gamma-carboxy prothrombin (DCP) is a useful prognostic factor in patients with hepatocellular carcinoma. World J Gastroenterol. 2009;15(5):489-493.