Association of Abnormal Plasma Bilirubin With Aggressive Hepatocellular Carcinoma Phenotype

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Cirrhosis-related abnormal liver function is associated with predisposition to hepatocellular carcinoma (HCC). It features in several HCC classification systems and is an HCC prognostic factor. The aim of the present study was to examine the phenotypic tumor differences in HCC patients with normal or abnormal plasma bilirubin levels. A 2,416-patient HCC cohort was studied and dichotomized into normal and abnormal plasma bilirubin groups. Their HCC characteristics were compared for tumor aggressiveness features, namely, blood alpha-fetoprotein (AFP) levels, tumor size, presence of portal vein thrombosis (PVT) and tumor multifocality. In the total cohort, elevated bilirubin levels were associated with higher AFP levels, increased PVT and multifocality, and lower survival, despite similar tumor sizes. When different tumor size terciles were compared, similar results were found, even among patients with small tumors. A multiple logistic regression model for PVT or tumor multifocality showed increased odds ratios for elevated levels of gamma glutamyl transpeptidase (GGTP), bilirubin, and AFP and for larger tumor sizes. We conclude that HCC patients with abnormal bilirubin levels had worse prognosis than patients with normal bilirubin. They also had an increased incidence of PVT and tumor multifocality, and higher AFP levels, in patients with both small and larger tumors. The results show an association between bilirubin levels and indices of HCC aggressiveness.

Two general groups of factors have been shown to significantly influence prognosis in hepatocellular carcinoma (HCC) patients. They are tumor aggressiveness factors, such as tumor size and number, presence of portal vein thrombosis (PVT), and elevated plasma alpha-fetoprotein (AFP) levels on the one hand, and liver factors, such as plasma levels of bilirubin, albumin, prothrombin time, gamma glutamyl transpeptidase (GGTP), alkaline phosphatase (ALKP), and aspartate

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aminotransferase (AST), on the other hand. Thus, tumor factors and liver microenvironmental factors are thought to independently contribute to survival. These two groups of influences are recognized in many HCC classification systems, such as those of Okuda, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer (BCLC), and Japan integrated staging (JIS) score (JIS).[1-5] The CLIP, BCLC, and JIS systems use the Child-Turcotte-Pugh (CTP) score[6] for evaluating liver failure, with emphasis on normal or abnormal bilirubin levels (CLIP, BCLC, JIS, CTP). More recently, inflammatory indices also have been shown to be prognostically significant.[7,8] In the present work, we extend our previous analyses of HCC phenotypes,[9,10] by examining the possible relationships between normal and abnormal plasma bilirubin levels and indices of HCC aggressiveness. We found that patients with abnormal bilirubin levels had increased markers of tumor aggressiveness.

METHODS

Data Collection

We retrospectively analyzed prospectively collected data in the Italian Liver Cancer (ITA.LI.CA) study group database of 2,416 HCC patients accrued through 2008 at 11 centers[11] who had full baseline tumor parameter data, including computed tomography scan information on maximum tumor diameter, number of tumor nodules and presence of PVT, and plasma AFP levels; blood counts (hemoglobin, white blood cells, platelets, prothrombin time); routine blood liver function tests (total bilirubin, AST, ALKP, GGTP, albumin); demographics (gender, age, alcohol history, presence of hepatitis B or C); and survival information. ITA.LI.CA database management conforms to Italian legislation on privacy and this study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for this retrospective study on de-identified patients was obtained from the institutional review boards of participating centers.

Statistical Methodology

Means and standard deviations (M ± SD) for continuous variables, and relative frequency for categorical variables, were used as indices of centrality and dispersion of the distribution.

Chi-square test for categorical variables, Kruskal-Wallis rank test, and Wilcoxon rank-sum test (Mann-Whitney test) for continuous variables was used to

Table 1. Comparison of HCC Patients Dichotomized by Total Bilirubin <1.5 or ≥1.5 mg/dL in the Total Patient Cohort

Parameter*	Total Bilirubin (mg/dL) <1.5 (n = 1,443)	Total Bilirubin (mg/dL) ≥1.5 (n = 973)	*P* Value†
Platelet count (x 10^9/L)	133.7 ± 70.8	101.8 ± 58.2	<.0001
Hb (g/dL)	13.3 ± 2.0	12.6 ± 2.1	<.0001
GGTP (IU/mL)	75.8 ± 89.7	87.3 ± 116.0	.02
ALKP (IU/mL)	279.7 ± 1636.3	323.1 ± 1355.1	<.0001
Total bilirubin (mg/dL)	0.9 ± 0.3	3.3 ± 3.7	<.0001
PT (%)	73.4 ± 28.4	64.3 ± 22.4	<.0001
Albumin (g/dL)	3.7 ± 0.6	3.2 ± 0.6	<.0001
AFP (ng/dL)	1669.2 ± 14552.8	2960.5 ± 27737.0	<.0001
AST (IU/L)	41.0 ± 51.2	53.3 ± 58.3	<.0001
MTD (cm)	4.0 ± 3.2	4.3 ± 3.7	.12
PVT (%)	124 (8.7)	144 (15.0)	<.001‖
No. of tumor nodules (>3) (%)	218 (16.0)	206 (23.1)	<.001‖
Survival time (%)			
1 yr	950 (74.0)	516 (59.3)	<.001§
2 yr	686 (53.5)	304 (34.9)	<.001§
3 yr	478 (37.3)	189 (21.7)	<.001§

* All values: Means ± SD
† Wilcoxon rank-sum (Mann-Whitney) test
‖ Chi-square test
§ test z for proportions.
Abbreviations: Hb, hemoglobin; MTD, maximum tumor diameter; PVT, portal vein thrombosis; AFP, alpha-fetoprotein; GGTP, gamma glutamyl transpeptidae; ALKP, alkaline phosphatase; AST, aspartate aminotransaminase.