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Deranged Lipid Profiles and Hepatocellular Carcinoma: Clinical Significance and Association

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Abstract

Background: The increasing incidence of hepatocellular carcinoma (HCC) is a challenging health problem worldwide with poor prognosis and limited treatment options. The association between metabolic factors and HCC has been documented, however, there is a shortage of data about this association in our locality. Therefore, we aimed to determine the pattern of lipid profile in cirrhotic patients with HCC and investigate the association between dyslipidemia and HCC.

Method: In this case-control hospital-based study, serum lipid profile [total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL)] was determined in 100 patients with cirrhosis and 100 patients with cirrhosis and HCC. Multivariate analysis of HCC risk factors was done.

Results: Metabolic syndrome, hypertriglyceridemia, hypercholesterolemia, high LDL, and combined dyslipidemia were significantly more frequent in HCC patients than non-HCC patients. Low HDL and dyslipidemia were significantly associated with the late HCC stages and LDL levels were significantly correlated with α-fetoprotein levels. There was a tendency towards increasing the values of the other lipid parameters in advanced stages. Metabolic syndrome and combined dyslipidemia were associated with HCC risk.

Conclusion: Deranged lipid profiles were common in HCC patients. Metabolic syndrome and combined dyslipidemia could be potential risk factors for HCC and may offer a useful strategy for risk stratification; thus, their control can reduce the HCC burden.

Keywords: Dyslipidemias, Hepatocellular carcinoma (HCC), Metabolic syndrome, Risk factors

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Introduction

Over the last decade, the global incidence of hepatocellular carcinoma (HCC) has rapidly increased with nearly 782,000 new cases annually.[1] It represents the sixth common cancer and the fourth cause of cancer-related mortality with about 746,000 annual deaths worldwide.[2-4] Although chronic hepatitis B (HBV), chronic hepatitis C (HCV), and alcoholic liver disease are the major risk factors for HCC, they do not fully explain this recent increase in HCC incidence.[5] Recently, several risk factors for HCC have been documented, such as non-alcoholic fatty liver disease (NAFLD), obesity, and diabetes mellitus (DM).[6-8]

Liver has a crucial role in lipid metabolism and transport. In addition, liver is a main source of the majority of plasma apolipoproteins, endogenous lipids, and lipoproteins, which depend on the integrity of cellular functions of liver. Hence, in severe liver disease, lipid metabolism is profoundly disturbed.[9] Several reports explored the association between aberrant blood lipid profiles (dyslipidemia) and cancer, including HCC. However, there were discrepancies in these reports, which may be due to the types of cancer or the related confounding factors, including life-style, diabetes, and obesity. In regard to HCC, the observed association with dyslipidemia remains elusive and inconsistencies, such as

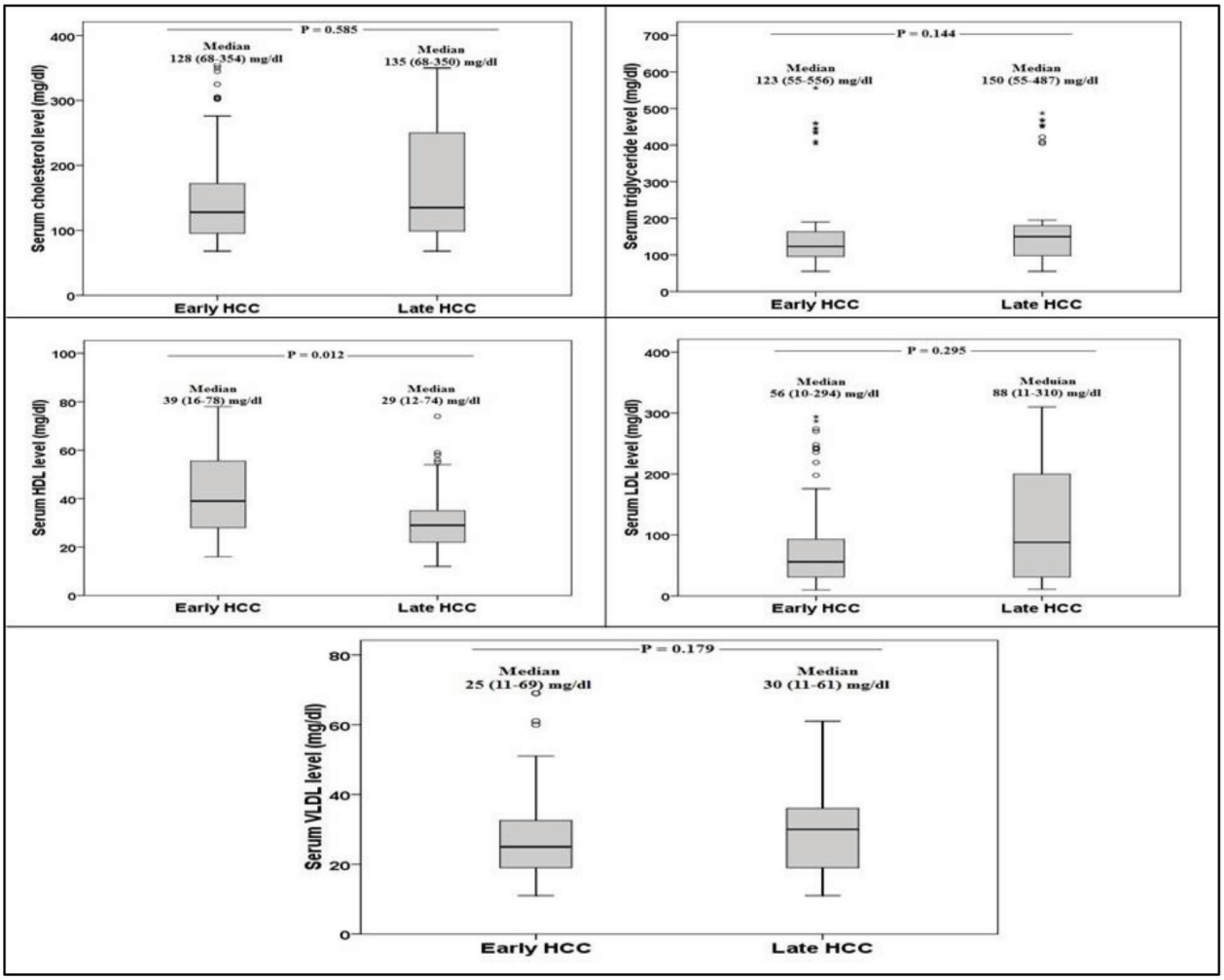

Figure 1. Comparison between BCLC stages of HCC regarding serum lipid profile showed that patients with late HCC had significantly lower serum HDL levels compared to those with early HCC (*P*= 0.012); however, no statistically significant differences were found between the two groups regarding other lipid parameters.

P-value < 0.05 was significant; BCLC; Barcelona Clinic Liver Cancer staging system; HCC: Hepatocellular carcinoma; HDL: High-density lipoprotein; LDL: Low-density

Table 1. Characteristics of cirrhotic patients with and without HCC

Variables	Total number of cirrhotics (n= 200)	Cirrhotics with HCC (n= 100)	Cirrhotics without HCC (n= 100)	*P*-value
Age (year)	62.3 ± 5	62.5 ± 5.4	61.98 ± 4.6	0.437
Sex				
Male/Female	141/59 (70.5/29.5%)	72/28 (72/28%)	69/31 (69/31%)	0. 755
Etiology of cirrhosis				
Hepatitis C virus	143 (71.5%)	72 (72%)	71 (71%)	0.202
Hepatitis B virus	28 (14%)	12 (12%)	16 (16%)	
Co- infections	25 (12.5%)	12 (12%)	13 (13%)	
None B none C	4 (2%)	4 (4%)	0 (0%)	
Systemic hypertension	102 (51%)	36 (36%)	28 (28%)	0.396
Diabetes mellitus	84 (42%)	20 (20%)	26 (26%)	0.310
Central obesity	85 (42.5%)	39 (39%)	46 (46%)	0.317
Metabolic syndrome	70 (35%)	41 (41%)	29 (29%)	0.044
Child-Pugh				
Classification	117/61/22	54/32/14	63/29/8	0.290
Class A/B/C	(58.5/30.5/11%)	(54/32/14%)	(63/29/8%)	
Bilirubin (mg/dl)	0.98 (0.6–14.6)	0.95 (0.7–14.6)	0.98 (0.6–7.2)	0.377
Albumin (mg/dl)	3.4 ± 0.9	3.4 ± 0.9	3.3 ± 0.9	0.264
AST (U/L)	39.5 (22–1800)	67.5 (22–1800)	37.5 (22–234)	0.019
ALT (U/L)	33 (21–351)	58 (22–351)	43 (21–211)	0.030
ALP (U/L)	3.4 ± 0.9	125 (67–658)	111 (61–467)	0.044
INR	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.2	0.923
AFP (ng/ml)	9 (2–8000)	556.5 (3–8000)	5 (2–9)	< 0.001
Hypercholesterolemia	33 (16.5%)	29 (29%)	4 (4%)	< 0.001
Hypertriglyceridemia	66 (33%)	39 (39%)	27 (27%)	0.071
Low HDL	119 (59.5%)	63 (63%)	56 (56%)	0.313
High LDL	36 (18%)	28 (28%)	8 (8%)	< 0.001
High VLDL	31 (15.5%)	16 (16%)	15 (15%)	0.845
Combined dyslipidemia	74 (37%)	44 (44%)	30 (30%)	0.040

Values were presented as mean ± standard deviation or median (range) or frequency (%). $P < 0.05$ was significant; AFP: Alpha feto-protein; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; HDL: High density lipoprotein; INR: International randomized ratio; LDL: Low-density lipoprotein; VLDL: Very-low-density lipoprotein; HCC: Hepatocellular carcinoma

positive or inverse association were found in various studies.[10-12]

In Egypt, HCC is the fourth prevalent cancer where the number of HCC patients increased two-fold over a decade.[13, 14] In addition, the major risk factor for HCC is chronic HCV infection. However, to our knowledge, the data about evaluating dyslipidemia as a potential risk for HCC are lacking in our locality. Therefore, we aimed to determine the pattern of lipid profiles in cirrhotic patients with HCC, to investigate the association between dyslipidemia and HCC, and to shed more light on this important issue gaining more interest worldwide.

Patients and Methods

Study design

This case-control, hospital-based study was carried out at Assiut University Hospital; a tertiary care teaching hospital, Assiut, Egypt, from January 2019 to January 2020. The study was approved by the Ethics Committee of Assiut University Hospital and was carried out according to the previsions of the Declaration of Helsinki. The ethical approval code was 17101185. An informed consent was obtained from all the participants prior to enrollment.

Study population

The study group compromised 200 adult patients with liver cirrhosis divided into two groups, 100 patients with HCC and 100 patients without HCC. All patients met the diagnostic

Table 2. Multivariate analysis of the predictors of HCC development in cirrhotic patients

	Odds ratio (95% CI)	*P*-value
Metabolic syndrome	1.70 (0.94 - 3.10)	0.050
AST	1.02 (0.99 - 1.05)	0.163
ALT	0.97 (0.93 - 1.02)	0.294
ALP	0.99 (0.98 - 1.03)	0.145
Hypercholesterolemia	0.97 (0.94 - 1.02)	0.235
High LDL	1.02 (0.98 - 1.06)	0.386
AFP	1.57 (1.25 - 2.02)	0.001
Combined dyslipidemia	1.86 (1.18 - 5.33)	0.041

P-value was significant if < 0.05; AFP: Alpha feto-protein; ALT: Alanine transaminase; AST: Aspartate transaminase; HCC: Hepatocellular carcinoma; LDL: Low-density lipoprotein; CI: Confidence interval; ALP: Alkaline phosphatase

criteria of liver cirrhosis by clinical, laboratory, and imaging findings. Furthermore, severity of liver disease was assessed using Child-Pugh score. The diagnosis of HCC was based on the triphasic computed tomography (CT) scan in accordance with the guidelines for the diagnosis and treatment of HCC.[15] The staging of HCC was assessed by the Barcelona Clinic Liver Cancer staging system (BCLC),[16] where stages 0, A, and B were known as early stage and stages C and D were known as late or advanced stage.

The patients consecutively enrolled between January 2019 and January 2020 at the Tropical Medicine and Gastroenterology Department, Assiut University Hospital, Egypt. The patients with the evidence of hepatic metastasis, previous HCC therapy, receiving lipid-lowering drugs, or antiviral drugs for B or C were excluded from the study.

Methods

At study entry, a thorough medical history and physical examination were taken for data collection, including age, sex, metabolic factors like diabetes, hypertension, life-style habits, alcohol consumption, medical history, and other related information.

Waist circumference to determine the central obesity was taken at the end of expiration at the midway point between the lower border of the lowest rib and the iliac crest horizontally. Imaging, including abdominal sonography and multi-slice CT (MSCT) was performed to determine liver and spleen size, ascites, and tumor site, size, number and metastasis.

Following an overnight fast, each patient underwent blood tests containing liver function tests, including albumin, bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP), INR, blood picture, alpha feto-protein (AFP), hepatitis B surface antigen (HBs Ag), antibody to hepatitis C virus (HCV-Ab) and lipid profile, including total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL).

Definitions

Central obesity was defined as waist circumference >101.6 cm (40 inches) for males and 88.9 cm (35 inches) for females.[17] Metabolic syndrome was defined as the presence of at least three of the following conditions: central obesity, dyslipidemia (hypertriglyceridemia and lowered HDL), hypertension, and impaired fasting glucose/DM.[17] Combined dyslipidemia was a disorder of lipoprotein metabolism (lipoprotein deficiency or overproduction). Dyslipidemias may be manifested through the elevation of the total cholesterol, LDL, triglyceride concentrations, and a decrease in HDL concentration in the blood.[18] Hypercholesterolemia was defined as a serum total cholesterol level ≥ 240 mg/dl.[19] Hypertriglyceridemia was defined as a serum triglyceride level ≥ 150 mg/dl.[17] High LDL was defined as a serum LDL level >160 mg/dl and > 70 mg/dl for DM.[19] Low HDL was defined as serum HDL level < 40 for males and < 50 mg/dl for females.[17] High VLDL was defined as a serum VLDL level > 40 mg/dl.[19]

Table 3. Comparison between metabolic factors and serum lipid parameters in patients with HCV- and HBV-related HCC

Variables	HCV-related cirrhotics with HCC (n= 72)	HBV-related cirrhotics with HCC (n= 12)	*P*-value
Hypertension	36 (50%)	4 (33.3%)	0.285
Diabetes mellitus	24 (33.3%)	2 (16.7%)	0.248
Central obesity	29 (40.3%)	4 (33.3%)	0.648
Metabolic syndrome	30 (41.7%)	4 (33.3%)	0.586
Hypercholesterolemia	22 (30.6%)	1 (8.3%)	0.110
Hypertriglyceridemia	32 (44.4%)	1 (8.3%)	0.018
Low HDL	45 (62.5%)	7 (58.3%)	0.783
High LDL	22 (30.6%)	1 (8.3%)	0.110
High VLDL	14 (19.4%)	0	0.094
Combined dyslipidemia	34 (47.2%)	3 (25%)	0.151

Values are presented as frequency (%). *P*–value < 0.05 was significant; HCC: Hepatocellular carcinoma; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very-low-density lipoprotein; HCV: Hepatitis C virus; HBV: Hepatitis B virus

Statistical analysis

We carried out statistical analyses using SPSS for windows version 16 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test of normality was performed to determine the normality of data. Continuous data was expressed as means ± standard deviation (SD) or median and (minimum-maximum) and was compared using Student's t-test or Mann-Whitney U test. Categorical variables were expressed as percentages and compared using chi-squared (X^2) or Fisher's exact probability test. Spearman coefficient correlation was used to find the correlation. Additionally, significant factors in univariate analysis were considered for inclusion in multiple regression analysis to determine risk factors for the development of HCC. For all analyses, $P < 0.05$ was statistically significant.

Results

Characteristics of the studied patients

200 patients with liver cirrhosis (100 with HCC and 100 without HCC) were included in the study. Their mean age was 62.3 ± 5 years and male sex was predominant (70.5%). Most patients had HCV-related cirrhosis (71.5%). None of those patients were alcoholic or had concomitant non-alcoholic steatohepatitis (NASH). Metabolic syndrome was present in 35% of cirrhotic patients, where its individual components; DM hypertension, dyslipidemia, and obesity, were present in 42, 51, 37, and 42.5%, respectively. Concerning the lipid profile, low HDL was the most common lipid change (59.5%). hypertriglyceridemia and hypercholesterolemia were present in 33% and 16.5%, respectively.

Further clinical and laboratory data of the studied patients and their subgroups were summarized in table 1.

Determination of risk factors for HCC

Compared with non-HCC group, AFP, AST, and ALT levels were significantly higher in patients with HCC ($P < 0.001$, $P = 0.02$ and $P = 0.03$, respectively). Moreover, univariate analysis indicated that metabolic syndrome ($P = 0.044$), hypercholesterolemia ($P < 0.001$), high LDL ($P < 0.001$), and combined dyslipidemia ($P = 0.04$) were significantly associated with HCC risk in cirrhotic patients as shown in table 1.

In the multivariate analysis, AFP ($P= 0.001$), combined dyslipidemia ($P = 0.041$), and metabolic syndrome ($P = 0.05$) were independent predictors of HCC development in cirrhotic patients. There were no statistically significant differences between both groups regarding other lipid parameters in spite of a tendency towards increased values in cirrhotic patients with HCC (Table 2).

In regard to metabolic risk factors and lipid profile in patients with HBV- and HCV-related HCC, hypertriglyceridemia was significantly more frequent in patients with HCV-related HCC ($P = 0.018$). However, no statistically significant differences were found between both groups regarding metabolic factors and other lipid parameters (Table 3).

Table 4. Comparison between demographic and clinical characteristics of cirrhotic patients with HCC regarding combined dyslipidemia

Variables	HCC with combined dyslipidemia (n= 44)	HCC without combined dyslipidemia (n= 55)	*P*-value
Age (year)	61.6 ± 5	63.2 ± 5.7	0.615
Sex			
Male/Female	29/15 (65.9/34.1%)	43/13 (76.8/23.2%)	0.229
Etiology of cirrhosis			
HCV infection	34 (77.3%)	38 (67.9%)	0.543
HBV infection	3 (6.8%)	9 (16.1%)	
Co-infection	5 (11.4%)	7 (12.5%)	
Non B, non C	2 (4.5%)	2 (3.6%)	
Ascites	19 (43.2%)	20 (35.7%)	0.447
Splenomegaly	26 (59.1%)	35 (62.5%)	0.729
Hepatomegaly	11 (25%)	18 (32.1%)	0.435
Child-Pugh classification			
Class A/B/C	23/26/5 (52.3/36.4/11.4%)	31/16/9 (55.4/28.6/16.1%)	0.637
WBCs (x 10^6/ml)	6.4 (1.8 - 21)	6.6 (1.7 - 19.3)	0.819
Hb (g/dl)	11.2 ± 3	11.5 ± 3.3	0.615
Platelets (x 10^6/ml)	179.5 (49-417)	130 (46-397)	0.154
Bilirubin (mg/dl)	1 (0.7-7.5)	0.9 (0.7-14.6)	0.604
Albumin (mg/dl)	3.5 ± 0.9	3.3 ± 0.9	0.447
AST (U/L)	40 (24-640)	68 (22-1800)	0.669
ALT (U/L)	33.5 (24-239)	35 (22-351)	0.532
ALP (U/L)	124.5 (67-567)	125.5 (69-658)	0.942
INR	1.2 ± 0.2	1.2 ± 0.3	0.893
AFP (ng/ml)	523 (3-5678)	578 (4-8000)	0.736
BCLC-HCC stages			
Early stages (0, A and B)	21 (47.7%)	38 (67.9%)	
Late stages (C and D)	23 (52.3%)	18 (32.1%)	0.042
Tumor site			
Right lobe/Left lobe/Both lobes	27/10/7 (61.4/22.7/15.9%)	38/10/8 (67.9/17.9/14.3%)	0.781
Tumor number			
Single/More than one	29/15 (65.9/34.1%)	46/10 (82.1/17.9%)	0.063
Tumor size (mm)	12 (2.3-56)	6 (1.5-64)	0.099

Values are presented as mean ± standard deviation or median (range) or frequency (%). *P*–value < 0.05 was significant; AFP: Alpha feto-protein; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BCLC: Barcelona Clinic Liver Cancer staging system; INR: International randomized ratio; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HBV: Hepatitis B virus, WBC: White blood cell; Hb: Hemoglobin

Association between dyslipidemia and characteristics of patients with HCC

Table 4 represents the characteristics of the studied patients with HCC based on the presence of combined dyslipidemia. We noticed that late HCC stages were significantly associated with combined dyslipidemia ($P = 0.042$). Regarding demographic, clinical and the other HCC characteristics, no statistically significant differences were found between the two groups ($P > 0.05$).

In patients with HCC, serum HDL levels were significantly lower in patients with late HCC than early HCC ($P = 0.012$). However, there were no statistical significant differences between the two groups regarding other lipid parameters despite a tendency towards increasing the values in advanced HCC stages as shown in figure 1. Additionally, serum HDL levels were negatively correlated with tumor number (rho= -0.320, $P = 0.046$). LDL levels were significantly correlated with AFP and (rho= 0.380, $P = 0.031$). However, no significant correlations were found between other lipid parameters and AFP, tumor size, or tumor number as summarized in table 5.

Discussion

This study corroborated metabolic syndrome, hypertriglyceridemia, hypercholesterolemia, combined dyslipidemia, and high LDL as predictors of HCC. The current work elucidated

Table 5. Correlation between serum lipid parameters and AFP

		Triglyceride	Cholesterol	HDL	LDL	VLDL
AFP	Correlation Coefficient (rho)	0.019	0.130	- 0.052	0.380	0.019
	P	0.791	0.067	0.462	0.031	0.788
Tumor size	Correlation Coefficient (rho)	0.045	0.027	- 0.110	0.046	0.059
	P	0.701	0.818	0.347	0.694	0.616
Tumor number	Correlation Coefficient (rho)	0.165	0.024	- 0.320	0.006	0.149
	P	0.101	0.811	0.046	0.956	0.140

P-value < 0.05 was significant; AFP: Alpha feto-protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein

that metabolic syndrome was associated with HCC risk (odds ratio= 1.7, 95% CI, 0.94-3.1). It was significantly more common in HCC patients than non-HCC patients, which was in line with earlier studies.[20-22] Welzel et al.[22] reported that metabolic syndrome was significantly associated with the increased HCC risk (odds ratio= 2.13; 95% CI, 1.96-2.31). Metabolic syndrome can promote liver carcinogenesis in several ways, including potential direct protumoral actions of insulin-resistance, obesity, and NAFLD.[6-8] Moreover, direct oncologic effects of a low-grade inflammatory response can lead to the loss of tumor suppression genes and the deregulation of several signaling pathways.[23]

Consistence with previous works,[24-27] we found that serum cholesterol levels were significantly higher in HCC patients than non-HCC patients and the highest levels were observed in late HCC stages. Higher levels can be attributed to paraneoplastic hypercholesterolemia, the loss of negative feedback mechanism for cholesterol, and impaired uptake of chylomicron remnants in malignant hepatocytes.[24-28] On the other hand, hypercholesterolemia may be related to malignant biliary obstruction and cholesterol overproduction by undifferentiated HCC cells, where more than 90% of cholesterol is released into the circulation.[26,27,29] Conversely, several studies reported that HCC patients had low cholesterol levels as tumor cells intake much exogenous cholesterol for cytomembrane synthesis, DNA duplication, and oncogene protein regulation.[30-32]

Unlike previous studies,[30,32] we found that serum LDL levels were significantly higher in HCC than non-HCC patients with a tendency towards increased values in late HCC stages. Our findings can be attributed to the reduced LDL receptors resulting in decreased LDL catabolism and increased LDL production in HCC patients with paraneoplastic hypercholesterolemia.[28,33]

Similar to Alsabti,[25] it was observed that hypertriglyceridemia was more frequent in HCC patients than non-HCC patients but with no statistical significance. In contrast, Motta et al.[30] reported that serum triglyceride levels decreased by 20%-30% in HCC patients. Moreover, some studies revealed that its levels in HCC were not significantly different compared with controls.[32,34] Therefore, these discrepancies in serum triglyceride levels in different studies may be an issue for further investigations.

Herein, while no difference between HCC and non-HCC patients regarding HDL levels was observed, lower levels were significantly associated with advanced HCC. Kanel et al.[35] revealed that patients with primary or metastatic liver cancers had remarkably decreased serum HDL levels due to the reduced biosynthesis in severe hepatocellular dysfunction. Ooi et al.[32] reported that low HDL may reflect the pathologic conditions and the severity of liver diseases.

We found that combined dyslipidemia was significantly higher in HCC patients than non-HCC patients and it was associated with an increased HCC risk of 1.86 (95% CI, 1.18-5.33). These results were concomitant with previous reports indicating the association of dyslipidemia with cancer development and progression.[10-12, 36]

In this study, hypertriglyceridemia was significantly more frequent in the HCV-related than the HBV-related HCC group and other lipid parameters implied trends towards a rise in values in the former one. Several authors assumed that chronic HCV infection was associated with viral steatosis that could be responsible for secondary

insulin resistance and systemic inflammation and thus an increased HCC risk.[37,38] Viral steatosis are shown to regress after a viral eradication.[39]

Combined dyslipidemias were positively related with BCLC stages of HCC; the higher the stage, the more frequent the dyslipidemia indicating that cancer cells can upregulate their lipogenic and lipolytic pathways for gaining lipids.[40] LDL levels were positively correlated with AFP, and HDL levels were negatively related with the HCC number. Moreover, other lipid parameters showed elevated levels but without statistical significance in advanced stages. These increased levels may be related to paraneoplastic syndrome which is associated with poor prognosis and reduced survival.[26,28] Several studies were in accordance with our findings and several others were not, thus indicating the complex role of dyslipidemia in HCC pathogenesis that warrants further evaluation.

This study had some limitations. It was a small-sized sample, single-center study, however, it was conducted in a tertiary care center where different stages of HCC can be evaluated. It was a case-control study, thereby making it difficult to determine whether lipid profile changes were the risk factors or sequelae of HCC, and if they were risk factors, it was difficult to verify how the duration of exposure to risk-factors could affect HCC development. Hence, large cohort studies will be emphasized to confirm these findings, to clarify their pathogenic mechanisms, and to assess their levels and impact on the prognosis upon HCC treatment.

Conclusion

In conclusion, metabolic syndrome and deranged lipid profiles were common in cirrhotic patients with HCC, particularly in those with HCV infection. Metabolic syndrome and combined dyslipidemia could be potential risk factors for HCC development in cirrhotic patients, which offer a useful risk-stratification strategy; therefore, their control can reduce the HCC burden.

Conflict of Interest

None declared.

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