

The Effect of Pre-transplant Lipid Profile on Post-transplant Hepatocellular Carcinoma Recurrence: Retrospective Single-Center Analysis

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ABSTRACT

Background: Plasma lipids have been shown to relate to tumor biology. We aimed to analyze the effect of pre-transplant plasma lipid profiles on post-transplant tumor recurrence in patients with hepatocellular carcinoma and to identify any possible relationship between the pre-transplant lipid profile with maximum tumor diameter, number of tumor nodules, tumor differentiation, portal vein invasion, or serum biomarker levels.

Methods: Patients with hepatocellular carcinoma who underwent liver transplants between 2006 and 2021 had data collected prospectively and were analyzed retrospectively. Patients who did not have lipid profile data before transplant and whose post-transplant follow-up period was <90 days were excluded. Patients who had pre-transplant plasma lipid data and whose post-transplant follow-up period was >90 days were included in this study (n = 254).

Results: Lower high-density lipoprotein cholesterol levels were found to be significantly associated with post-Tx recurrence (38 vs 29.5, $P < .001$) and were also significantly associated with macroscopic portal vein thrombosis (39 vs 30.4, $P < .021$). There was no significant association between plasma lipids and tumor differentiation. Higher high-density lipoprotein cholesterol levels were significantly associated with good overall and disease-free survivals ($P = .024$ and $P = .001$).

Conclusion: Pre-transplant low plasma high-density lipoprotein cholesterol levels were significantly associated with portal vein thrombosis and poor post-transplant overall and disease-free survivals.

Keywords: Fat, HCC, HDL cholesterol, relapse, transplant, tumor thrombosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally with 841 080 new cases in a year and the third most common cause of cancer-related deaths with 781 631 global deaths.¹ Tumor recurrence following surgery is still a most important prognostic factor for decrease in survivals, and to date, multiple biomarkers, including alpha-fetoprotein (AFP), Des gamma carboxy prothrombin (DCP)/ protein induced by vitamin K absence or antagonist-II (PIVKA-II), Gamma glutamyl transferase (GGT), and Neutrophile to lymphocyte ratio (NLR) have been shown to predict HCC recurrence.²⁻⁷ The relationship between plasma lipid levels and HCC has been previously studied, and a significant association was demonstrated with prognosis.⁸ Preoperative serum lipid profiles have been studied in patients who were treated with resection, but not in liver transplant (LT) patients, to our knowledge. In the

current study, we aimed to evaluate a possible predictive role of serum lipid profiles on survival in HCC patients who underwent LT.

MATERIALS AND METHODS

Patient Selection

We have performed 2929 liver transplantations between March 2002 and March 2021, of which 440 were for HCC and were analyzed retrospectively from our database which is prospectively recorded. Patients who survived more than 90 days post-transplant and patients whose pre-transplant blood lipid profiles were available were the subjects of this study (n = 254). Patients with post-transplant follow-up lower than 90 days (n = 50) or whose pre-transplant blood lipid profiles were not available (n = 136) were excluded. Demographics, tumor data, and patient survival were analyzed.

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We previously published our pre- and post-transplant management of HCC patients.^{2,3} Pre-transplant last laboratory parameters and demographics were recorded, and tumor parameters were recorded according to explant pathology report. Blood lipid profiles include triglyceride, cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, and blood samples were taken while the patients were fasting. Cut off levels of the lipid parameters were used according to our routine clinical biochemistry laboratory cut off levels (for cholesterol, 199 mg/dL; for HDL, 40 mg/dL; for LDL, 130 mg/dL; for VLDL, 40 mg/dL; for triglyceride, 150 mg/dL). This study was approved by İnönü University Institutional Review Board (Approval no: 2020/1266).

Statistical Analysis

Categorical (qualitative) variables were expressed as counts and percentages. Comparisons of groups were made by Pearson's chi-square test for categorical variables. Continuous (quantitative) variables were summarized by median, minimum, and maximum values. Comparisons between 2 groups were performed by Mann-Whitney *U* test, and Kruskal-Wallis test was used to compare more than 2 groups for quantitative variables. Correlation between quantitative variables was examined by Spearman's rho correlation coefficient. Kaplan-Meier survival analysis was used to estimate overall survival (OS) and disease-free survival (DFS) of the patients, and log-rank test was used for survival comparisons. Follow-up period was defined as the interval between LT until the date of the last visit to the outpatient department for living patients or until the date of death of the patient. Time

to disease recurrence was defined as the interval between the LT until the date a lesion that appeared to be a tumor was detected by biochemical (AFP) and radiological examination and/or a lesion diagnosed as HCC in the new liver or in another region of the patient. Statistical tests were considered significant when the corresponding *P* value was less than 5%. All statistical analyses were performed using The Statistical Package for Social Sciences (SPSS) version 25.0 software (IBM Corp.; Armonk, NY, USA).

RESULTS

Patient Demographics, Tumor Characteristics, and Survival

Clinical and tumor characteristics of the 254 HCC patients of this study are summarized in Table 1. Mean follow-up was 3140.01 ± 124.23 days (2896.53-3383.5; 95% CI). The 1-, 3-, and 5-year OS and DFS of 254 HCC patients were 89%, 77.5%, and 72.2% versus 84.5%, 72.6%, and 71.6%, respectively, and post-transplant tumor recurrence was 15.7% (*n* = 40). Patients within Milan criteria for LT were 54.7% (139/254), and serum AFP levels of ≤ 200 ng/mL were 81.1% (*n* = 206/254). Patients with macroscopic portal vein thrombosis (macroPVT) were 9.4% (24/254), while patients with microscopic venous invasion (microPVI) were 33.9% (*n* = 86). Median body mass index (BMI) was 25.9 (16.3-46.9), and major underlying liver disease was viral hepatitis in 79.9% of patients (*n* = 203). Loco-regional therapies such as radiofrequency ablation, resection, transarterial chemoembolization, transarterial radioembolization before transplantation were performed in 48 patients (18.9%).

Correlation Between Pre-transplant Lipids and Post-transplant HCC Recurrence

We compared the recurrence positive (*n* = 40) and negative patients (*n* = 214) in terms of significant differences in pre-transplant blood lipid parameters and found that only the low HDL cholesterol was significantly associated with recurrence (29 vs 38.9 mg/dL, respectively, *P* < .001). There were no significant differences between tumor recurrence and blood triglyceride, LDL, VLDL, and cholesterol levels (Table 2).

Correlation Between Pre-transplant Lipids and Venous Invasion

Patients were divided into 3 subgroups according to venous invasion, as no-invasion (*n* = 144), microPVI (*n* = 86), and macroPVT (*n* = 24). When we compared the venous invasion groups according to lipid parameters, we found that

Main Points

- We analyzed the pre-Tx last serum lipid profile of the hepatocellular carcinoma (HCC) patients in terms of post-Tx prognosis.
- Pre-Tx lower high-density lipoprotein (HDL) levels were significantly associated with portal vein invasion (30 vs. 39.4 mg/dL, *P* = .021) and post-Tx HCC recurrence (29 vs. 38.9 mg/dL, *P* < .001).
- When we dichotomized the patients according to HDL cut off of 40 mg/dL, patients in HDL ≥ 40 group had significantly better liver function tests, lower C reactive protein (CRP), Neutrophile to lymphocyte ratio (NLR), maximum tumor diameter, and portal vein thrombosis (PVT) rates, and better overall and disease-free survival rates than patients in HDL < 40 group.
- Serum HDL cholesterol level can be used as a prognostic biomarker in HCC patients after liver transplantation.

Table 1. Demographics and Tumor Characteristics of All Cohort (n = 254)

Parameter	n	Median	Minimum	Maximum		n	%
Age	254	56.0	2.0	72.0	Etiology, viral hepatitis	203	79.9
BMI	249	25.9	16.3	46.9	AFP ≤ 200 ng/mL	206	81.1
MELD	254	12.0	6.0	37.0	GGT ≤ 104 IU/L	166	65.4
Glucose	254	104.0	65.0	521.0	Differentiation		
Lipids profile					Well	107	42.1
Triglyceride	254	82.0	17.0	376.0	Moderate	109	42.9
Cholesterol	254	136.0	12.0	372.0	Poor	38	15
HDL	254	36.9	3.9	84.0	Venous invasion		
LDL	253	81.2	5.9	304.0	None	144	56.7
VLDL	254	16.5	3.4	115.6	MicroPVI	86	33.9
Laboratory parameters					MacroPVT	24	9.4
Albumin	254	2.9	1.20	5.2	Loco-regional therapy	48	18.9
Total bilirubin	254	1.68	.23	33.8	Recurrence, positive	40	15.7
AST	254	53.5	9.0	589.0	AFP, alpha-fetoprotein; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; MicroPVI, microscopic venous invasion; MacroPVT, macroscopic portal vein thrombosis; MTD, maximum tumor diameter; MELD, Model for End-stage Liver Disease.		
ALT	253	39.0	12.0	675.0			
ALP	254	115.0	31.0	799.0			
INR	202	1.29	0.82	4.1			
GGT	253	70.0	13.0	1396.0			
LDH	204	231.5	112.0	1538.0			
Plt	254	104.0	16.0	528.0			
Tumor morphology							
AFP	254	12.8	0.2	20 179.0			
MTD	254	3.0	0.1	24.0			
Number of nodules	254	1.0	1.0	36.0			
Inflammatory parameters							
NLR	254	2.5	0.3	26.8			
PLR	254	80.2	9.7	683.3			
CRP	150	.667	0.15	305.70			
		n		%			
Gender, Male		219		86.2			
Child							
A		101		39.8			
B		108		42.5			
C		45		17.7			
MELD ≤ 14		175		68.9			
Milan criteria, in		139		54.7			
Malatya criteria, in		166		65.4			
Extended Malatya criteria, in		178		70.1			

HDL cholesterol levels were significantly different from other lipid parameters in this respect ($P = .021$). The median HDL cholesterol level was 30.4 (min-max, 5–61.3 mg/dL) in patients with macroPVT and was 36.25 (3.9–84) in microPVI patients and 39 (3.9–70.8) in the no-invasion patients, and these differences were significant (Table 3).

Correlation Between Pre-transplant Lipids and Hepatocellular Carcinoma Differentiation

Patients were divided into 3 subgroups according to tumor differentiation, as well differentiated ($n = 107$), moderately well differentiated ($n = 109$), and poorly differentiated ($n = 38$). We found no significant differences ($P > .05$) (Supplementary Table 1) among the differentiation groups according to lipid parameters.

Correlation Between Pre-transplant Lipids and Tumor Biology

Maximum tumor diameter (MTD), number of tumor nodules, and pre-transplant AFP levels are well-known parameters that predict tumor aggressiveness in HCC patients.⁹ We previously described the Malatya and Extended Malatya Criteria for LT in HCC patients and found that pre-transplant serum GGT level is also a significant

Table 2. Lipid Profile and Post-Tx Recurrence

All Cohort (n = 254)	Recurrence Negative, (n = 214)	Recurrence Positive, (n = 40)	
Pre-Tx Lipids Profile	Median (Min-Max)	Median (Min-Max)	P
Triglyceride (mg/dL) (0-150)	84.5 (17-376)	76.5 (51-243)	.330
Cholesterol (mg/dL) (0-199)	136 (12-250)	134 (41-372)	.852
HDL cholesterol (mg/dL) (40-60)	38.9 (3.9-84)	29 (5-59.08)	<.001
LDL cholesterol (mg/dL) (30-130)	79.8 (5.9-185.6)	83 (15.2-304)	.176
VLDL cholesterol (mg/dL) (10-40)	16.9 (3.4-115.6)	15.3 (10.2-49)	.393

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

prognostic parameter.^{2,3} We therefore analyzed the correlation between these parameters (MTD, tumor numbers, AFP and GGT levels) and lipid parameters, separately, and found a weak correlation between MTD and cholesterol, HDL, and LDL (R^2 : coefficient of determination was insufficient to explain this relation). Similarly, a weak correlation was found between GGT and triglyceride, cholesterol, LDL, and VLDL levels (Supplementary Table 2).

Correlation Between Pre-transplant Lipid Parameters and Survival

We categorized the lipid parameters according to the normal range of values in the laboratory and calculated the OS and DFS as follows:

Survivals according to HDL ≥ 40 mg/dL versus HDL < 40 mg/dL

1-, 3-, and 5-year OS and DFS in patients with high HDL (HDL ≥ 40 mg/dL) were 94.7%, 82.6%, 79% and 94.7%, 83.6%, 83.6%, respectively, while in patients with low HDL (HDL < 40 mg/dL) were 85.3%, 73.7%, 70.1% and 78%, 65.8%, 64.4%, respectively ($P = .024$ and $P = .001$).

High-density lipoprotein levels were significantly associated with both OS and DFS (Figure 1).

Survivals according to triglyceride ≤ 150 mg/dL versus triglyceride > 150 mg/dL

1-, 3-, and 5-year OS in patients with low vs high triglyceride (≤ 150 vs >150 mg/dL) were 90.7%, 79.5%, 75.4% vs 72.4%, 59.3%, 59.3% and $P = .042$, while 1-, 3-, and 5-year DFS in patients with low versus high triglyceride (≤ 150 vs >150 mg/dL) were 85.7%, 74.4%, 73.4% vs 72.7%, 54.3%, 54.3% and $P = .059$. Triglyceride levels were significant in OS and almost significant in DFS (Figure 2).

Survivals according to VLDL ≤ 40 mg/dL versus VLDL > 40 mg/dL

1-, 3-, and 5-year OS in patients with low versus high VLDL (≤ 40 vs >40 mg/dL) were 90%, 79%, 75% vs 73.3%, 55.9%, 55.9% and $P = .051$, while 1-, 3-, and 5-year DFS in patients with low versus high VLDL (≤ 40 vs >40 mg/dL) were 85.3%, 74.2%, 73.2% vs 73.3%, 48.6%, 48.6% and $P = .048$. Very low-density lipoprotein levels were significant in DFS and almost significant in OS (Figure 3).

Table 3. Lipid Profile and Venous Invasion

All Cohort (n = 254)	Venous Invasion			P
	None (n = 144)	Microscopic (n = 86)	Macroscopic (n = 24)	
Pre-Tx lipids profile	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Triglyceride (mg/dL) (0-150)	82 (39-376)	86 (17-290)	75.5 (36-173)	.494
Cholesterol (mg/dL) (0-199)	135.5 (18-250)	136.5 (12-288)	141 (70-372)	.755
HDL cholesterol (mg/dL) (40-60)	39.0 ^a (3.9-70.8)	36.25 ^a (3.9-84)	30.4 ^b (5-61.3)	.021
LDL cholesterol (mg/dL) (30-130)	80.3 (5.9-179)	79.9 (7.3-197.6)	93.2 (35-304)	.265
VLDL cholesterol (mg/dL) (10-40)	16.7 (7.8-115.6)	16.9 (3.4-58)	15.1 (7.2-43.2)	.590

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

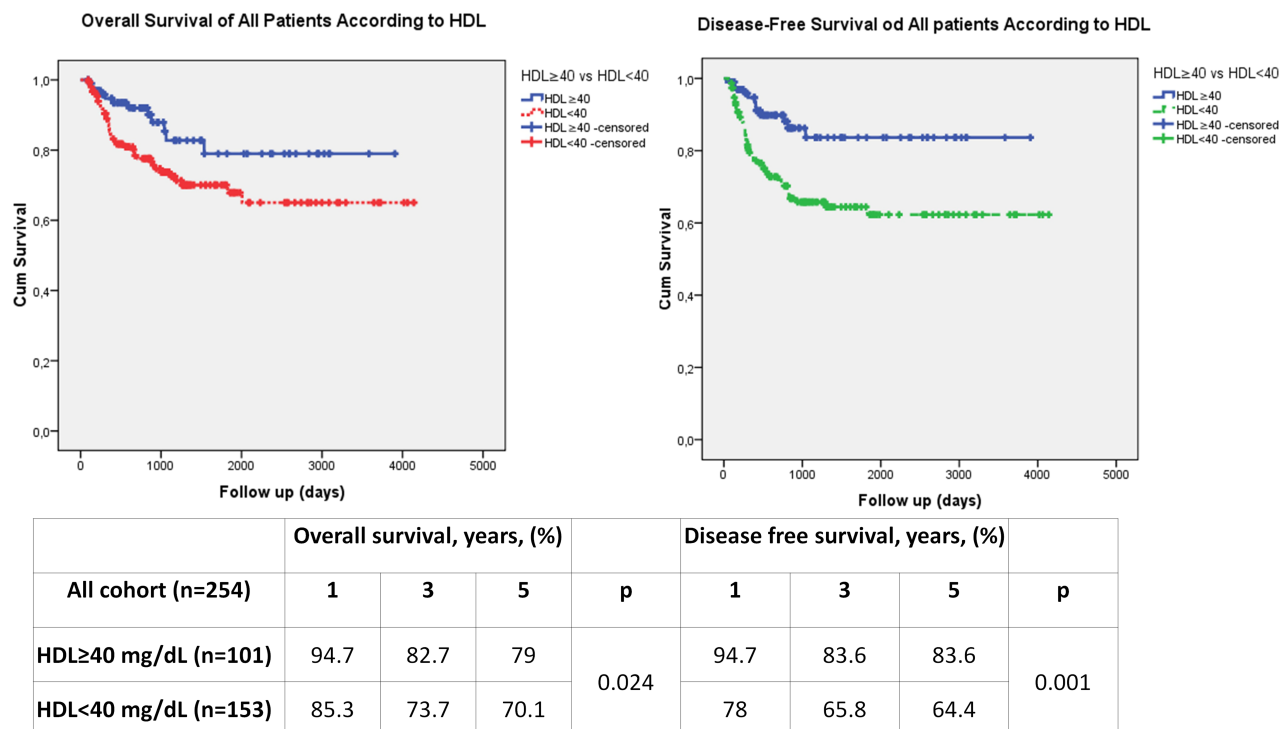


Figure 1. Survivals according to HDL ≥ 40 mg/dL vs HDL < 40 mg/dL. HDL, high-density lipoprotein.

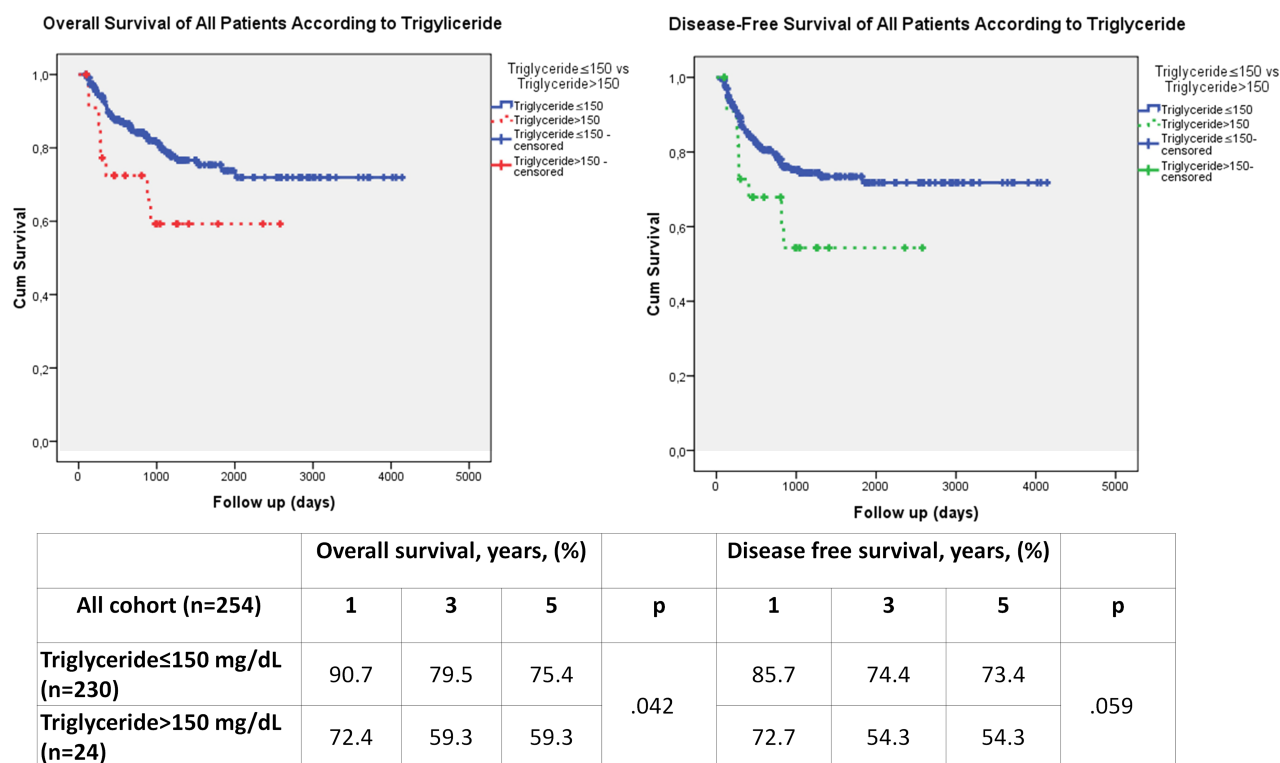


Figure 2. Survivals according to triglyceride ≤ 150 mg/dL vs triglyceride > 150 mg/dL.

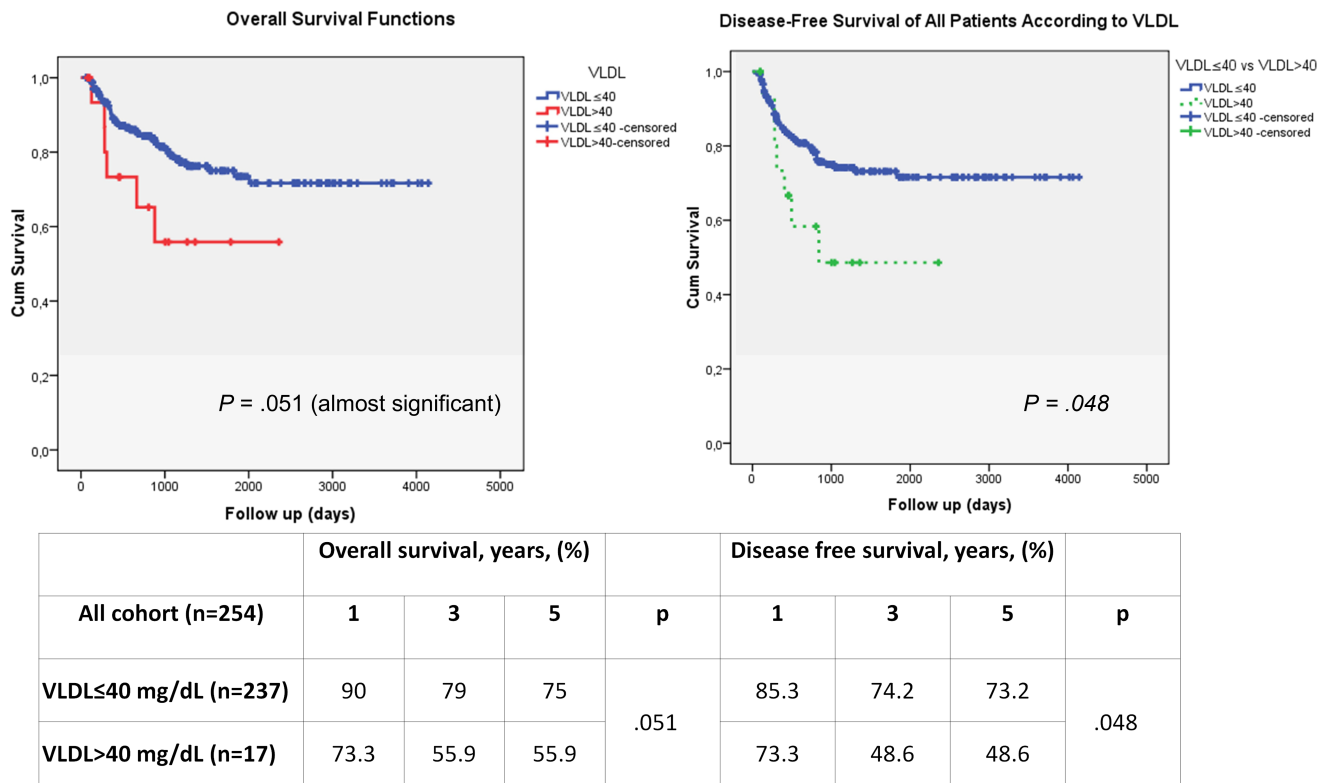


Figure 3. Survivals according to VLDL ≤40 mg/dL vs VLDL >40 mg/dL. VLDL, very low-density lipoprotein.

Low-density lipoprotein and cholesterol levels were not significant either for OS or for DFS.

Comparison of Clinical and Tumor Characteristics According to High-Density Lipoprotein Levels

After finding significant survival advantages in patients with high HDL levels, we compared the clinical and tumor characteristics of the HCC patients with high and low HDL. Cholesterol and albumin levels were significantly higher, and MTD, total bilirubin, aspartate amino transferase (AST), lactate dehydrogenase (LDH), CRP, and NLR were significantly lower in patients with the high HDL as compared with the low HDL group (Table 4).

Regarding portal vein invasion, 66.3% of patients without any portal vein invasion were in the long-survival high HDL group, but only 33.7% in this group had portal vein invasion. These differences were significantly different (Table 5, $P = .012$).

DISCUSSION

In general, plasma lipid levels tend to decrease with the severity of liver disease, but different etiologies of liver

injury may have variable effects on the lipid profile. In a study comparing the lipid profile in patients with alcoholic and non-alcoholic cirrhosis, it is emphasized that HDL and LDL levels can be used as a marker in the severity of liver damage for patients with non-alcoholic cirrhosis, but only the triglyceride level can be used as a marker in alcohol-induced cirrhosis.¹⁰ Therefore, more detailed studies on cirrhosis and lipid profiles are needed.

Significant changes in HDL levels were also found in studies investigating the relationship between serum lipid levels and HCC.^{8,11,12} Several mechanisms have been suggested regarding the relationship between HCC aggressiveness and serum HDL levels. First, HDL plays a role in intracellular cholesterol balance, and serum HDL levels were observed inversely with the cholesterol levels in tumor tissue. Low serum HDL levels can be associated with increased cholesterol metabolism, as cholesterol consumption and storage will increase in growing tumor tissue.¹³ Secondly, regarding HDL metabolism, it can be regulated by cytokines. Increased levels of HDL have been related to decreased circulating levels of proinflammatory cytokines, such as interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor (TNF- α), whereas decreased

Table 4. Clinical Characteristics in Patients with Low or High HDL Levels

	HDL < 40 (n = 153)	HDL ≥ 40 (n = 101)	
	Median (Min-Max)	Median (Min-Max)	P
Triglyceride (mg/dL)	84 (36-376)	82 (17-339)	.114
Cholesterol (mg/dL)	124 (12-372)	152 (80-288)	<.001
LDL cholesterol (mg/dL)	77.8 (7.3-304)	85.9 (5.9-197.6)	.099
VLDL cholesterol (mg/dL)	17 (7.2-115.6)	16 (3.4-67.8)	.053
BMI	26 (16.35-46.88)	25.71 (16.4-41)	.567
Albumin	2.6 (1.2-5.2)	3.1 (1.6-4.3)	<.001
Total bilirubin	2.15 (0.3-33.83)	1.23 (0.23-7.51)	<.001
AST	62 (19-589)	47 (9-538)	.002
ALT	39 (12-366)	39 (5-675)	.291
ALP	118 (43-799)	108 (31-383)	.115
GGT	70 (13-1396)	70 (15-412)	.535
LDH	250.5 (121-1538)	207 (112-441)	.002
CRP	1.14 (0.253-51)	0.33 (0.16-305.7)	<.001
NLR	2.77 (0.7-26.83)	2.13 (0.3-7.32)	.004
PLR	87.54 (9.7-683.33)	73.59 (19.4-355)	.161

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

HDL levels have been linked with elevated levels of anti-inflammatory cytokines, for example, IL-10.¹⁴ These proinflammatory cytokines are thought to increase cell proliferation and inhibit apoptosis.¹⁵ Another aggressiveness mechanism concerns change in tumor membrane lipids that alter membrane fluidics and thus modulate growth factor signaling, as well as HCC invasiveness properties.^{16,17}

In our study, when patients with low and high HDL were compared, we found that total bilirubin, AST, LDH were higher, but albumin was lower, which reflects worse liver function and more fibrosis in patients with low HDL. We also found higher inflammatory parameters (CRP and NLR levels) and worse tumor morphology, higher MTD and higher PVT rates in the low HDL patients. These findings, similar to the literature, support the idea that HDL is effective in antagonizing tumorigenesis through both lower inflammation and cholesterol consumption

Table 5. Tumor Characteristics in Patients with Low or High HDL Levels

	HDL < 40 (n = 153)	HDL ≥ 40 (n = 101)	
	Median (Min-Max)	Median (Min-Max)	P
Pre-Tx last AFP	14.5 (0.4-20179)	11.4(0.2-6388)	.300
MTD (cm)	3.1 (0.1-24)	2.5(0.1-14)	.027
Number of nodules	2 (1-36)	1 (1-27)	.230
	n (%)	n (%)	
Number of nodules			
≤2	108 (70.6)	71 (70.3)	.960
>2	45 (29.4)	30 (29.7)	
PVT			
None	77 (50.3)	67 (66.3)	.012
Micro + Macro	76 (49.7)	34 (33.7)	

AFP, alpha-fetoprotein; HDL, high-density lipoprotein; MTD, maximum tumor diameter; PVT, portal vein thrombosis.

mechanisms in tumor tissue. Serum lipid profiles may vary with metabolic syndrome and obesity, in association with high BMI values, and this variability may affect the results. However, when patients with high and low HDL were compared in our study, both groups were similar with respect to BMI.

Plasma lipid profiles and HCC recurrence after radical resection were studied previously, and low cholesterol and low HDL levels were found to be significantly associated with poor outcomes.⁸ In our study, involving only LT patients, we found that only pre-transplant low HDL levels were associated with poor outcomes (low DFS and low OS rates) and that pre-transplant HDL levels were significantly associated with post-transplant HCC recurrence (Table 2 and Figure 1). These results show that pre-transplant HDL level might serve as a prognostic marker for post-transplant HCC recurrence.

In a study of 521 non-transplant HCC patients investigating tumor aggressiveness and lipid profiles, it was found that portal vein thrombosis was higher in those with low HDL (8.51 vs 19.03, $P = .0002$).¹¹ In our study, HDL levels were also found to be significantly lower in patients with vascular invasion. The median HDL cholesterol level was 30.4 (min-max 5-61.3 mg/dL) in patients with macroPVT,

while 36.25 (3.9-84) in microPVI and 39 (3.9-70.8) in no-invasion groups, and these differences were significant with $P = .021$. Changes in tumor membrane lipids alter membrane fluidics and thus growth factor signaling, as well as HCC properties such as tumor invasiveness.^{16,17}

Serum HDL levels were previously found to be associated with recurrence and tumor aggressiveness in HCC patients.^{8,9} In the current study, we found that a similar relationship was also valid in LT patients. It was therefore predicted that low HDL levels would result in poor DFS and OS rates. In our study, HDL <40 mg/dL was associated with a significantly lower survival rate in both 5-year DFS and OS results comparing with HDL $\geq$ 40 mg/dL (5-year DFS was 64.4% vs 83.6%, $P = .001$ and 5-year OS 70% vs 79%, $P = .024$, respectively).

The survival analysis according to triglyceride cut off 150 mg/dL, in those with TG <150 mg/dL had significantly better OS but not significant in DFS, whereas compared to VLDL $\leq$ 40 vs >40 mg/dL, while OS was almost significant in patients with VLDL $\leq$ 40 mg/dL, DFS was significantly better. These survival outcomes in the TG and VLDL levels seemed to reach significance as the sample size increased.

The strength of this study is the extension of serum HDL levels for prognostication for liver transplantation patients with HCC. They also confirm the findings of others of the relationship between elevated levels of serum HDL and better outcomes. By examining the associated tumor factors, we suggest a plausible explanation for this survival and recurrence finding. Limitations of this study are its retrospective design, small number of patients, and the requirement for external validation. Furthermore, although we found associations for HDL with tumor aggressiveness parameters, whether they were cause or consequence cannot be definitively established. However, these findings have potential use for HCC patient prognostication. Especially combination of HDL with other serum biomarkers such as AFP, DCP, GGT, and so on can increase its predictive power on prognosis. Given the prognostic significance of HDL levels that was found in this study, future HCC management paradigms might need to take this into account.

CONCLUSION

The current study showed that pre-transplant low serum HDL cholesterol levels are significantly associated with portal vein invasion and poor post-transplant OS and

DFS. Serum HDL cholesterol levels might be used as a prognostic biomarker for HCC patients who undergo liver transplantation.

Ethics Committee Approval: This study has been approved by İnönü University Institutional Review Board (Approval no: 2020-1266).

Informed Consent: No informed consent was needed because of the retrospective non-interventional study design.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – V.I., B.I.C., S.Y.; Design – V.I., B.I.C., S.Y.; Supervision – S.Y.; Resources – V.I., B.I.C.; Materials – V.I., H.G.B.; Data Collection and/or Processing – V.I., S.U., V.E.; Analysis and/or Interpretation – H.G.B., V.I., S.U., V.E.; Literature Search – V.I., V.E.; Writing Manuscript – V.I., B.I.C., S.U.; Critical Review – V.I., B.I.C., S.Y.

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Supplementary Table 1. Lipid Profile and Differentiation

	Differentiation			<i>P</i>
	Well (n = 107)	Moderate (n = 109)	Poor (n = 38)	
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Triglyceride (mg/dL) (0-150)	85 (44-243)	81 (17-376)	83 (36-258)	.897
Cholesterol (mg/dL) (0-199)	138 (23-250)	136 (12-372)	133.5 (60-229)	.562
HDL cholesterol (mg/dL) (40-60)	39.2 (3.9-84)	36 (3.9-69.1)	35.8 (5-59.7)	.163
LDL cholesterol (mg/dL) (30-130)	82.9 (5.9-185.6)	81.4 (7.3-304)	79.3 (29.6-154)	.922
VLDL cholesterol (mg/dL) (10-40)	17 (8.8-115.6)	16.2 (3.4-75.2)	16.5 (7.2-51.6)	.854

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Supplementary Table 2. Correlation Analysis Between Lipids and MTD, Number of Nodules, GGT, AFP

n = 254	Triglyceride (mg/dL)	Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	VLDL Cholesterol (mg/dL)
MTD (cm)					
<i>r_s</i>	0.001	0.145	−0.134	0.233	0.010
<i>P</i>	.982	.021	.033	<.001	.873
<i>R</i> ²		2.1%	1.8%	5.4%	
Number of nodules					
<i>r_s</i>	0.079	−0.004	−0.113	0.068	0.071
<i>P</i>	.210	.956	.073	.280	.263
<i>R</i> ²					
GGT					
<i>r_s</i>	0.210	0.282	0.112	0.228	0.211
<i>P</i>	.001	<.001	.076	<.001	.001
<i>R</i> ²	4.4%	8%		5.2%	4.4%
Pre-Tx last AFP					
<i>r_s</i>	0.047	−0.062	−0.079	−0.051	0.043
<i>P</i>	.454	.325	.208	.415	.492
<i>R</i> ²					

r_s, Spearman's rank correlation coefficient; *R*², coefficient of determination. AFP, alpha-fetoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; MTD, maximum tumor diameter. Statistical tests were considered significant when the corresponding *P* value was <5%.