Research Article

ADMA in patients with liver dysfunction

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The correlation of ADMA with proinflammatory, liver injury and cancer biomarkers in patients with liver dysfunction

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Abstract

Background and Aim: Asymmetric dimethylarginine (ADMA) is an enzyme involved in vascular tone, blood pressure, and platelet activation. Serum ADMA levels are increased in liver diseases such as liver cirrhosis, hepatitis, and acute liver failure. The aim of our study was to assess the correlation of ADMA with proinflammatory, liver injury, and cancer biomarkers in patients with liver dysfunction of various etiologies.

Materials and Methods: We analyzed the demographic and clinical data, including serum ADMA concentration and other biochemical markers such as albumin, platelet count, international normalized ratio, bilirubin, and others in patients with hepatitis, compensated and decompensated liver cirrhosis, and hepatocellular carcinoma. The one-way ANOVA, Student's t-test, Mann-Whitney U test, univariate, and multivariate correlations were performed, and a p-value <0.05 was set as significant.

Results: In n=83 analyzed patients, we observed a negative correlation of ADMA with albumin concentration (p=0.049). We found a negative correlation between ADMA and platelet count in n=31 patients with compensated liver cirrhosis (p=0.022). We observed no significant correlations of ADMA with proinflammatory and cancer biomarkers in patients with hepatitis, compensated and decompensated liver cirrhosis, and hepatocellular carcinoma.

Conclusion: ADMA can potentially be used as a subsidiary marker of disease progression in patients with liver dysfunction. Our research suggests that ADMA cannot be useful in detecting hepatocellular carcinoma (HCC).

Keywords: ADMA; biomarker; liver dysfunction; cirrhosis; hepatocellular carcinoma; hepatitis.

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Introduction

Asymmetric dimethylarginine (ADMA) is an inhibitor of nitric oxide synthase (NOS), competing with L-arginine, which is necessary to synthesize nitric oxide (NO).[1] Elevated ADMA serum concentrations lead to vasoconstriction, increased platelet aggregation, enhanced cell adhesion to the endothelium, and vascular muscle cell proliferation.[2] Consequently, ADMA has been identified as a risk marker for cardiovascular diseases, and its concentration above the upper normal range has been identified as a risk factor for multiorgan dysfunction in critically ill patients.[3,4] Furthermore, some researchers suggest that reducing serum ADMA levels could lower the risk of atherosclerosis and diabetes mellitus or serve as a treatment for hypertension.[5]

Free ADMA, along with symmetric dimethylarginine (SDMA), is produced during the proteolytic degradation of methylarginines. ADMA is primarily metabolized in the liver and kidneys and excreted by these organs. It is degraded to citrulline and dimethylamine by dimethylarginine dimethylaminohydrolase (DDAH), an enzyme predominantly found in the liver, kidneys, and pancreas.[1] Therefore, in chronic kidney disease (CKD), an elevation of serum ADMA concentration can occur, which is considered an independent mortality risk factor in CKD patients.[6] Moreover, serum ADMA accumulation is observed in patients with viral hepatitis, non-alcoholic fatty liver disease (NAFLD), and acute liver failure (ALF).[4,7,8] Higher plasma levels of ADMA are associated with liver cirrhosis, although not all metabolic pathways of NO and its connections with ADMA in the cirrhotic liver are understood. On one hand, liver cirrhosis is associated with vasodilation due to higher NO activity, but the activity of endothelial NO synthase (eNOS) is decreased. The study by Lluch et al.[9] may suggest a different regulation of eNOS in the liver and in the splanchnic vessels. Another mechanism may be due to impaired DDAH activity, leading to elevated ADMA concentrations.[10]

In patients with end-stage liver disease, cardiovascular risk is elevated with an increase in serum concentration of ADMA, NO, fasting glucose, HDL cholesterol, and the absence of hepatocellular carcinoma (HCC).[11] Elevated serum ADMA levels are also associated with the onset of multi-organ failure (MOF).[4]

The aim of this study was to assess the correlation of ADMA with proinflammatory, liver injury, and cancer biomarkers in patients with liver dysfunction, including hepatitis, compensated and decompensated liver cirrhosis, and hepatocellular carcinoma of various etiologies, to evaluate its potential use as a subsidiary marker in these liver diseases.

Table 1. Baseline data of all analyzed patients

	Mean	IQR	Median	SD	Minimum	Maximum
Age	56.3	15.0	57.0	13.4	29.0	87.0
ADMA						
Normal range: 0.4–0.75 µmol/L	0.8	0.3	0.5	3.4	0.0	31.0
VCAM-1						
Normal range: 20.5–2318.9 ng/ml	199.1	151.7	193.5	89.1	21.9	335.6
AFP						
Normal range: 2–12 ng/ml	332.3	90.8	6.9	1741.6	2.1	12500.0
CRP						
Normal range :<10.0 mg/l	17.2	24.2	7.8	21.4	0.0	77.4
CEA						
Normal range :<5.0 ng/ml	5.5	1.1	2.3	13.4	0.1	87.9
Ca 19.9						
Normal range: <33.0 U/ml	20.6	13.2	10.7	42.0	2.9	339.4
PLT						
Normal range: 139–387 G/L	136.9	120.5	127.0	85.4	12.0	539.0
INR						
Normal range: 0.77–1.43	1.2	0.2	1.2	0.3	0.8	2.5
Bilirubin						
Normal range: 3–22 µmol/L	59.7	39.2	32.5	84.5	8.1	518.7
ALT						
Normal range: 4–50 U/L	149.9	62.5	60.0	335.0	14.0	2276.0
AST						
Normal range: 10–59 U/L	147.3	106.5	74.0	247.5	20.0	1540.0
ALP						
Normal range: 38–126 U/L	176.6	165.5	135.5	123.6	53.0	618.0
GGTP						
Normal range: 15–73 µmol/L	204.9	125.5	97.0	354.5	12.0	2716.0
Albumin						
Normal range: 35–55 g/L	34.9	13.5	35.0	8.7	16.2	56.9
Total cholesterol						
Normal range: <5.0 mmol/L	4.9	0.4	4.8	1.4	2.2	10.3
LDL						
Normal range: <2.5 mmol/L	3.0	0.0	3.0	0.8	0.9	6.1
HDL						
Normal range: >1.0 mmol/L	1.4	0.0	1.4	0.5	0.5	3.5
TG						
Normal range: <1.7 mmol/L	1.5	0.4	1.4	0.6	0.7	3.4

SD: Standard deviation; IQR: Interquartile range; ADMA: Asymmetric dimethylarginine; VCAM-1: Vascular cell adhesion molecule 1; AFP: Alpha-fetoprotein; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; PLT: Platelet count; INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGTP: Gamma-glutamyl transferase; LDL: Low-density lipoproteins; HDL: High-density lipoproteins; TG: Triglycerides.

Materials and Methods

Blood samples were taken from patients admitted to our department with hepatitis, compensated and decompensated liver cirrhosis, and hepatocellular carcinoma of various etiologies. We analyzed demographic data and serum concentrations of ADMA (ELISA Cat. REA201/96 Enzyme Immunoassay for the Quantitative Determination of Endogenous ADMA in serum or plasma), vascular cell adhesion molecule 1 (VCAM-1) (BioSource International VCAM-1 ELISA kit), alpha-fetoprotein (AFP), C-reactive protein (CRP), carcinoembryonic antigen (CEA), cancer antigen 19-9 (Ca 19-9), platelet count (PLT), international normalized ratio (INR), bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGTP), albumin, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides (TG). The two-sample Student's t-test or Mann-Whitney U test were used to evaluate differences in mean values among quantitative variables. The one-way ANOVA test was performed to evaluate differences in mean values of analyzed biomarkers' levels. Correlations

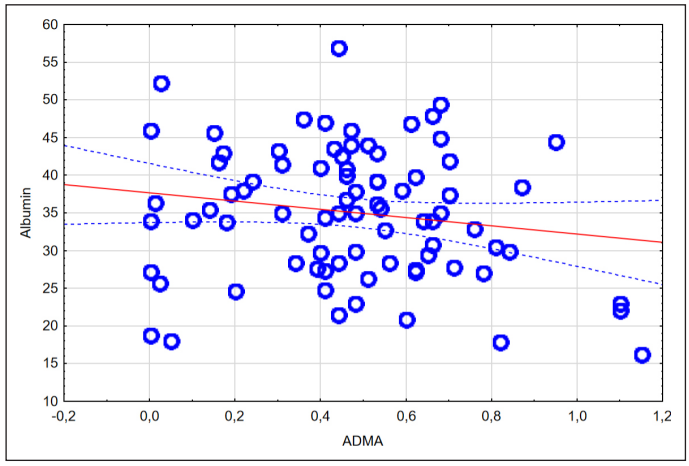

Figure 1. Scatterplot of ADMA and albumin concentrations among all patients.

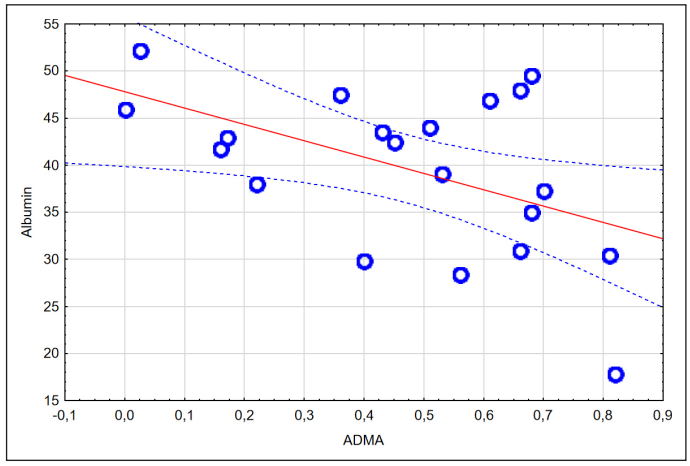

Figure 2. Scatterplot of ADMA and albumin concentrations in patients with hepatitis.

between quantitative variables were assessed using the Spearman correlation coefficient and multivariate linear regression. The p-value was set at <0.05. All statistical analyses were performed using Python 3.7 software and the Statistica 13.1 program (StatSoft Poland, Kraków, Poland).

Results

The study included 83 patients: 37 females and 46 males, with a mean age of 56.3 (range 29–87 years). There were 32 patients with compensated liver cirrhosis and 31 with decompensated cirrhosis. The etiologies included autoimmune hepatitis (AIH; n=4), ethanol cirrhosis (ETH; n=10), hepatitis B virus (HBV) infection (n=14), coinfection of HBV and hepatitis C virus (HBV/HCV; n=4), hepatitis C virus (HCV; n=28), and primary biliary cirrhosis (PBC; n=3). Hepatocellular carcinoma (HCC) was confirmed in 10 patients: 2 with compensated and 7 with decompensated liver cirrhosis. Among the 20 patients with hepatitis were AIH (n=3), ETH (n=1), HBV (n=6), HCV (n=8), and PBC (n=2). The baseline data of the analyzed patients are presented in Table 1.

Patients were divided into three groups for analysis according to various biomarkers. Data from patients diagnosed with HCC were compared separately from those without an HCC diagnosis (Table 2).

Post-hoc tests were performed to evaluate differences in mean concentrations of VCAM-1, platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin between the patient groups. A significant difference in mean VCAM-1 concentration was observed between patients with compensated and decompensated liver cirrhosis (p=0.012) and between patients with hepatitis and compensated cirrhosis (p=0.003). Significant differences in PLT count were also noted between patients with compensated and decompensated liver cirrhosis (p=0.001) and between those with hepatitis and decompensated cirrhosis (p=0.001). Significant differences in mean ALT concentrations appeared among patients with hepatitis and decompensated cirrhosis (p=0.004) and between those with compensated and decompensated cirrhosis (p=0.031). Moreover, significant differences were seen in mean AST concentrations between patients with hepatitis and decompensated liver cirrhosis (p=0.020), and in albumin concentrations between patients with hepatitis and decompensated cirrhosis (p<0.001) and between those with compensated and decompensated cirrhosis (p=0.002). No other mean differences reached statistical significance.

Univariate and multivariate correlations of ADMA with other biomarkers were further analyzed. Multivariate linear regression was adjusted for age, gender, and patient category (hepatitis, compensated, and decompensated liver cirrhosis). A statistically significant multivariate correlation was found between ADMA and albumin concentrations. The results are presented in Table 3 and Figure 1.

Univariate and multivariate correlations of ADMA with other biomarkers were also analyzed independently among the groups of patients. For these analyses, multivariate linear regression was adjusted for age and gender. A statistically significant univariate correlation of ADMA with albumin concentrations was found in patients with hepatitis, but this significance was not retained after adjusting for age and gender. A significant multivariate correlation was observed between ADMA concentration and PLT count among patients with compensated liver cirrhosis. These results are presented in Table 4, Figure 2, and Figure 3.

Discussion

In our study, we sought to define the significance of serum ADMA levels and its correlation with various biomarkers to evaluate it as a potential subsidiary marker of liver diseases.

In the analyzed group of patients, we observed that compensated liver cirrhosis was associated with elevated serum ADMA concentrations, which were not observed in patients with hepatitis or decompensated liver cirrhosis. Available data indicate that ADMA levels are increased in patients with liver cirrhosis, alcoholic hepatitis, and acute liver failure (ALF), and are higher in patients with decompensated than in compensated liver cirrhosis.[4,12] According to a paper by Karakecili et al.[7] serum ADMA levels are significantly higher in patients with chronic active hepatitis B compared to inactive HBV carriers and a control group. Similarly, Lluch et al.[13] report that in patients with chronic hepatitis C without signs of acute inflammatory activity, serum ADMA concentrations remain unchanged compared to a control group. Mookerjee et al.[14] also suggest that patients with alcoholic hepatitis superimposed on cirrhosis have higher ADMA values compared to patients without inflammation. Due to the small study population, we did not perform an analysis of ADMA concentration in patients with various hepatitis etiologies.

A platelet count and albumin concentration, among other basic serum laboratory tests, are used to identify disease progression in patients with chronic liver diseases.[15] According to a study by Surana et al.,[16] platelets

Table 2. Mean results of analyzed biomarkers in patients with hepatitis, compensated and decompensated liver cirrhosis

	Hepatitis (n=20)	Compensated liver cirrhosis (n=32)	Decompensated liver cirrhosis (n=31)	p	HCC (n=10)	No HCC (n=73)	p
Age mean (range) years	52.0 (31.0–87.0)	57.0 (35.0–86.0)	58.0 (29.0–81.0)	0.254	65.2 (51.0–82.0)	55.0 (29.0–87.0)	**0.020**
ADMA mean (range) Normal range: 0.4–0.75 µmol/L	0.5 (0.0–0.8)	1.4 (0.1–31.0)	0.5 (0.0–1.1)	0.445	0.5 (0.0–1.2)	0.9 (0.0–31.0)	0.278
VCAM-1 mean (range) Normal range: 20.5–2318.9 ng/ml	166.7 (30.2–317.3)	181.4 (21.9–314.8)	238.1 (116.7–335.6)	**0.006**	226.2 (67.6–318.7)	195.4 (21.9–335.7)	0.183
AFP mean (range) Normal range: 2–12 ng/ml	43.5 (3.0–450.0)	365.6 (2.1–10000.0)	484.3 (2.7–12500.0)	0.676	2558.3 (92.1–12500.0)	27.4 (2.1–121.9)	<**0.001**
CRP mean (range) Normal range: <10.0 mg/l	11.4 (0.1–63.9)	16.5 (0.1–71.8)	21.7 (0.1–77.4)	0.240	21.1 (0.1–70.5)	16.7 (0.1–77.4)	0.431
CEA mean (range) Normal range: <5.0 ng/ml	3.0 (1.7–12.4)	5.5 (0.1–87.9)	7.3 (0.3–65.1)	0.531	6.7 (0.1–33.5)	5.4 (0.3–87.9)	0.373
Ca 19.9 mean (range) Normal range: <33.0 U/ml	10.3 (2.9–26.2)	23.8 (2.9–339.4)	24.1 (2.9–155.0)	0.452	36.2 (3.6–155.0)	18.5 (2.9–339.4)	**0.017**
PLT mean (range) Normal range: 139–387 G/L	173.6 (22.0–290.0)	153.7 (36.0–539.0)	95.8 (12.0–332.0)	**0.002**	115.5 (36.0–239.0)	139.8 (12.0–539.0)	0.240
INR mean (range) Normal range: 0.77–1.43	1.2 (0.9–2.2)	1.2 (0.8–2.5)	1.3 (1.0–2.1)	0.328	1.2 (1.0–1.6)	1.3 (0.9–2.5)	0.281
Bilirubin mean (range) Normal range: 3–22 µmol/L	75.8 (8.1–354.7)	46.5 (12.3–244.8)	63.2 (8.6–518.7)	0.465	39.1 (10.1–67.0)	62.6 (8.1–518.7)	0.494
ALT mean (range) Normal range: 4–50 U/L	382.1 (21.0–2276.0)	99.7 (14.0–724.0)	52.0 (16.0–93.0)	**0.001**	78.7 (33.0–141.0)	159.7 (14.0–2276.0)	0.138
AST mean (range) Normal range: 10–59 U/L	286.3 (20.0–1540.0)	116.5 (25.0–741.0)	89.5 (20.0–372.0)	**0.013**	122.3 (33.0–270.0)	150.8 (20.0–1540.0)	0.081
ALP mean (range) Normal range: 38–126 U/L	132.5 (55.0–358.0)	185.7 (53.0–618.0)	195.9 (61.0–459.0)	0.177	164.4 (71.0–432.0)	178.3 (53.0–618.0)	0.469
GGTP mean (range) Normal range: 15–73 µmol/L	283.2 (12.0–2716.0)	234.2 (23.0–1378.0)	124.1 (14.0–543.0)	0.248	111.7 (14.0–317.0)	217.7 (12.0–2716.0)	0.302
Albumin mean (range) Normal range: 35 to 55 g/L	39.6 (17.9–52.3)	36.6 (21.6–47.0)	30.2 (16.2–56.9)	<**0.001**	30.5 (16.2–39.8)	35.5 (17.9–56.9)	0.637
Total cholesterol mean (range) Normal range: <5.0 mmol/L	5.2 (3.3–8.0)	5.0 (2.1–10.3)	4.6 (2.2–7.1)	0.229	4.6 (3.4–5.8)	4.9 (2.2–10.3)	0.300
LDL mean (range) Normal range: <2.5 mmol/L	3.2 (2.2–6.1)	3.0 (1.0–4.7)	3.0 (0.9–5.1)	0.529	2.8 (1.0–3.3)	3.1 (0.9–6.1)	0.395
HDL mean (range) Normal range: >1.0 mmol/L	1.4 (0.5–2.3)	1.6 (0.5–3.5)	1.4 (0.7–2.7)	0.166	1.5 (1.4–2.1)	1.4 (0.5–3.5)	0.159
TG mean (range) Normal range: <1.7 mmol/L	1.5 (0.8–3.4)	1.4 (0.8–3.2)	1.6 (0.7–3.3)	0.639	1.3 (1.0–1.4)	1.6 (0.7–3.4)	0.220

HCC: Hepatocellular carcinoma; ADMA: Asymmetric dimethylarginine; VCAM-1: Vascular cell adhesion molecule 1; AFP: Alpha-fetoprotein; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; PLT: Platelet count; INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGTP: Gamma-glutamyl transferase; LDL: Low-density lipoproteins; HDL: High-density lipoproteins; TG: Triglycerides.

performed significantly better in identifying cirrhosis compared to other examined biomarkers such as AST, ALT, albumin, etc. In our research, we observed a negative correlation between platelet counts and serum ADMA levels in patients with compensated liver cirrhosis, suggesting that ADMA could potentially be used as an additional biomarker in this disease. Albumin is synthesized exclusively by the liver, thus serum albumin levels are reduced in acute and chronic liver disease.[17] It is a factor related to steatohepatitis, fibrosis, and cirrhosis.[18] Available data also suggests that albumin levels are lower in patients with acute and higher in chronic viral hepatitis of different etiologies compared to healthy individuals.[19] In our study population, we saw a negative correlation of ADMA and albumin concentration. Since both lower albumin levels and higher ADMA levels are associated with the progression of liver diseases, serum ADMA concentrations could possibly serve as a marker of liver disease progression.[4,15]

Table 3. Correlation of ADMA with other biomarkers

Variable	Univariate r^2	Univariate p	Multivariate linear regression p
VCAM-1	0.017	0.246	0.070
AFP	0.001	0.842	0.341
CRP	0.007	0.461	0.251
CEA	0.001	0.856	0.343
Ca 19-9	0.001	0.807	0.280
PLT	0.011	0.342	0.088
INR	0.006	0.476	0.265
Albumin	0.023	0.171	**0.049** r=**0.364** r^2=**0.132**

ADMA: Asymmetric dimethylarginine; VCAM-1: Vascular cell adhesion molecule 1; AFP: Alpha-fetoprotein; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; PLT: Platelet count; INR: International normalized ratio.

Table 4. Correlation of ADMA with other biomarkers depending on the category of patients

Category	Variable	Univariate correlation coefficient r^2	Univariate p	Multivariate linear regression p
Hepatitis	VCAM-1	0.013	0.634	0.501
	AFP	0.087	0.206	0.305
	CRP	0.104	0.165	0.441
	CEA	0.099	0.176	0.282
	Ca 19-9	0.034	0.437	0.398
	PLT	0.028	0.484	0.513
	INR	0.186	0.058	0.172
	Albumin	**0.247**	**0.026**	0.176
Compensated liver cirrhosis	VCAM-1	0.051	0.216	0.069
	AFP	0.000	0.908	0.219
	CRP	0.016	0.486	0.234
	CEA	0.001	0.873	0.233
	Ca 19-9	0.002	0.820	0.121
	PLT	0.036	0.299	0.022 r=**0.536** r^2=**0.287**
	INR	0.020	0.439	0.192
	Albumin	0.105	0.070	0.060
Decompensated liver cirrhosis	VCAM-1	0.036	0.307	0.398
	AFP	0.058	0.192	0.252
	CRP	0.033	0.331	0.413
	CEA	0.000	0.999	0.514
	Ca 19-9	0.001	0.885	0.517
	PLT	0.039	0.289	0.391
	INR	0.000	0.987	0.479
	Albumin	0.029	0.358	0.397
Hepatocellular carcinoma	VCAM-1	0.118	0.331	0.057
	AFP	0.051	0.529	0.057
	CRP	0.188	0.211	0.075
	CEA	0.084	0.417	0.072
	Ca 19-9	0.148	0.272	0.079
	PLT	0.000	0.993	0.053
	INR	0.115	0.338	0.058
	Albumin	0.131	0.303	0.060

ADMA: Asymmetric dimethylarginine; VCAM-1: Vascular cell adhesion molecule 1; AFP: Alpha-fetoprotein; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; PLT: Platelet count; INR: International normalized ratio.

ADMA is significantly elevated in the plasma of cancer patients. Current literature mentions its elevated level in prostate, colon, stomach, and other cancers.[20] However, in hepatocellular carcinoma (HCC), ADMA levels are decreased due to the induced expression of DDAH, which catabolizes ADMA.[21] Plasma concentrations of biomarkers AFP, Ca 19-9, and CEA are significantly more elevated in patients with primary hepatic cancer compared to patients with liver cirrhosis and healthy control groups.[22] Our research seems to be consistent with current knowledge. In our study, the group of patients with HCC had lower ADMA concentration compared to individuals with no HCC diagnosis, but that difference was not statistically significant. However, plasma levels of AFP and Ca 19-9 were significantly higher in patients with HCC. In our research, we did not observe a correlation between the mentioned cancer biomarkers and ADMA.

We were not able to find statistically significant differences between other analyzed parameters and/or their correlation with serum ADMA levels. According to Pirisi et al.[23] VCAM-1 concentrations are elevated in liver diseases, and patients with acute hepatitis or cirrhosis have higher VCAM-1 levels than those with mild chronic liver disease, and VCAM-1 concentrations appear to reflect the severity of the liver disease but do not correlate with its etiology. Another analyzed marker was INR, which is the earliest and most accurate marker of liver failure – in liver diseases, hepatic synthesis is dysfunctional, resulting in increased INR. Bilirubin is a nonspecific marker of liver dysfunction and is not a sensitive marker of liver injury.[24] Bilirubin, ASP, ALT, and ALP can be useful in defining the source of liver damage – for example, elevated ALT and ASP in disproportion to ALP and bilirubin can suggest HCC.[25] In patients with cirrhosis, serum triglyceride, total, LDL, and HDL cholesterol levels are notably decreased and correlate with the severity of the cirrhosis.[26] Furthermore, a study by Manka et al.[27] suggests that HDL levels are significantly higher in patients with ALF caused by acetaminophen intoxication, compared to other analyzed etiologies. CRP values can indicate the probability of future decompensation in liver cirrhosis patients or rehospitalization.[28]

Many researches concerning liver diseases and ADMA levels that are currently available involved a limited number of participants. For example, a study by Czepiel et al. included 114 patients, a study by Karakecili et al. – 90 patients, a study by Mookerjee et al. – only 10 patients, and a study by Lluch et al. – only 46 patients.[7,13,14,29,30] All this suggests that the importance of ADMA is yet to be learned, and researchers should be encouraged to involve larger groups of patients in their studies on ADMA in liver diseases.

We understand that due to the limited number of patients involved in the research, many possible correlations between different biomarker values could not be discovered. The study, however, points out that such correlations may exist and therefore it is possible that ADMA can be found useful in thoroughly analyzing the condition of patients with liver diseases. We strongly believe that this subject requires further and broader research to evaluate the clinical significance of assessing serum ADMA levels.

Conclusion

ADMA can potentially be used as a subsidiary marker of disease progression in patients with underlying liver diseases. Furthermore, our research suggests that ADMA cannot be useful in detecting HCC.

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