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酒精性脂肪肝合并幽门螺杆菌感染患者颈动脉内膜中层厚度与炎性、氧化应激因子的相关性

王敏, 周源, 李常伟, 周泽伟, 刘慧

(重庆市大足区人民医院消化内科, 重庆 402360)

[摘要] 目的: 探讨酒精性脂肪肝(alcoholic fatty liver disease, AFLD)合并幽门螺杆菌(*Helicobacter pylori*, Hp)患者血清中炎症和氧化应激因子与颈动脉内膜中层厚度(carotid intima-media thickness, CIMT)的关系。方法: 选取2018年1月至2019年2月于重庆市大足区人民医院门诊检查及住院的168例男性患者, AFLD合并Hp感染患者为A组, AFLD患者为B组, Hp感染患者为C组, 两种病症均无记为D组。颈部超声测量各组双侧CIMT, 检测各组血脂、血糖(glucose, GLU)、肝功能指标、炎症及氧化应激因子水平, 分析CIMT与各指标的相关性。结果: A组CIMT显著增厚且发生率提高($P < 0.05$), 患者BMI、血液中总胆固醇(TC), 三酰甘油(TG), ApoA1, ApoB, 丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶(AST)及 γ -GT均显著高于对照组($P < 0.05$)。A组白介素6(IL-6)、C反应蛋白(C-reactive protein, CRP)水平明显升高, 丙二醛(malondialdehyde, MDA)、超氧化物歧化酶(superoxide dismutase, SOD)水平降低, 与D组相比, 差异有统计学意义($P < 0.05$)。AFLD合并Hp感染患者CIMT与年龄, BMI, TC, TG, IL-6, CRP均呈显著正相关($P < 0.05$), 与MDA, SOD呈负相关($P < 0.05$)。结论: 年龄, BMI, TC, TG, IL-6, CRP及MDA, SOD与AFLD合并Hp感染患者CIMT均呈显著相关, 而相关程度可能跟疾病所处的阶段有关。

[关键词] 酒精性脂肪肝; 幽门螺杆菌; 颈动脉内膜中层厚度; 炎症; 氧化应激

Correlation between carotid intima-media thickness and inflammatory and oxidative stress factors in patients with alcoholic fatty liver complicated with *Helicobacter pylori* infection

WANG Min, ZHOU Yuan, LI Changwei, ZHOU Zewei, LIU Hui

(Department of Gastroenterology, People's Hospital of Dazu District, Chongqing 402360, China)

Abstract **Objective:** To investigate the relationship between serum inflammatory, oxidative stress factors and carotid intima-media thickness (CIMT) in patients with alcoholic fatty liver complicated with *Helicobacter pylori* (Hp)

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通信作者 (Corresponding author): 周源, Email: 845223997@qq.com

infection. **Methods:** A total of 168 male patients who were examined and hospitalized in our hospital from January 2018 to February 2019 were selected as the research objects. Patients with alcoholic fatty liver disease complicated with *Hp* infection were recorded as group A, patients with alcoholic fatty liver disease were recorded as group B, and patients with *Hp* infection was recorded as group C, neither of which was recorded as group D. CIMT of bilateral common carotid artery in each group was detected by cervical ultrasound, and the levels of blood lipid, blood glucose, liver function, inflammation and oxidative stress factors in each group were detected, and the correlation between CIMT and the indicators was analyzed. **Results:** In group A, CIMT was significantly thickened and the incidence was increased ($P<0.05$). BMI, TC, TG, ApoA1, ApoB, ALT, AST and γ -GT in the patients were significantly higher than those in the control group ($P<0.05$). The levels of IL-6, CRP in group A were significantly higher than that in group D ($P<0.05$), while the levels of MDA, SOD were lower than that in group D ($P<0.05$). Patients with alcoholic fatty liver disease complicated with *Hp* infection showed significant positive correlation with age, BMI, TC, TG, IL-6 and CRP ($P<0.05$), and negative correlation with MDA and SOD ($P<0.05$). **Conclusion:** Age, BMI, TC, TG, IL-6, CRP and MDA, SOD were significantly correlated with carotid intima-media thickness in patients with alcoholic fatty liver complicated with *Hp* infection, and the degree of correlation might be related to the different stages of the disease.

Keywords alcoholic fatty liver disease; *Helicobacter pylori*; carotid intima-media thickness; inflammation; oxidative stress

近年来, 心脑血管疾病“四高一多”的特点越来越突出, 即发病率、病死率、致残率、复发率高, 并发症多。动脉粥样硬化(atherosclerosis, AS)为其主要的病理基础, 肠道病毒、疱疹病毒、肺炎衣原体、幽门螺杆菌(*Helicobacter pylori*, *Hp*)等感染性疾病是其重要的致病因素^[1-3]。*Hp*感染可造成全身性炎症反应及脂质等代谢紊乱, 动脉内膜损伤, 诱发AS, 最终导致心脑血管疾病^[4]。非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)是AS发生的关键因素, 关于酒精性脂肪肝(alcoholic fatty liver disease, AFLD)对AS的影响报道甚少, 而AFLD并伴有*Hp*感染是临床上常见病例^[5]。因此, 本研究通过检测AFLD合并*Hp*感染患者血清中的炎症和氧化应激因子, 以探讨其与颈动脉内膜中层厚度(carotid intima-media thickness, CIMT)的关系, 为预防AS性疾病提供指导。

1 对象与方法

1.1 对象

选取2018年1月至2019年2月于重庆市大足区人民医院门诊检查及住院的168例男性患者作为研究对象, 其中AFLD合并*Hp*感染的患者为A组(60例), AFLD但无*Hp*感染患者为B组(54例), *Hp*感染但NAFLD患者为C组(20例), NAFLD且未被*Hp*感染的患者为D组(34例)。患者年龄

36~66(47.24±6.83)岁。纳入标准参照中华医学会肝脏病学分会脂肪肝和酒精性肝病学组于2010年制定的《酒精性肝病诊疗指南》^[6]: 一般有超过5年的长期饮酒史, 折合乙醇量男性 ≥ 40 g/d, 或2周内折合乙醇量 > 80 g/d的大量饮酒史[换算公式: 乙醇量=饮酒量 \times 乙醇含量 $\times 0.8$]; 腹部超声显示肝内管道结构不清, 肝近场回声强于肾且呈弥漫性增强(“明亮肝”), 肝远场回声逐渐衰减, 具备其中两项表现者为弥漫性脂肪肝; HBV-DNA阴性、HBs Ab阳性患者; 采用¹³C呼气试验检测*Hp*, 吸光度值 ≥ 4 诊断为阳性。排除标准: 年龄 ≥ 70 岁或 < 25 岁; 不能表达自身感受或精神异常; 血清HBs Ag和HBV-DNA均阳性; 淤胆性肝炎、隐源性肝炎、自身免疫性肝炎或HCV感染; 肝功能失代偿期者; 合并肝性脑病、肝癌、消化道出血、水电解质及酸碱平衡紊乱、感染等严重并发症; 原发性或继发性神经、内分泌、心脑血管、肺、肾及血液系统疾病; 备孕、妊娠期及哺乳期妇女。本研究经患者及家属知情同意, 并经重庆市大足区人民医院医学伦理委员会审核批准。

1.2 CIMT 超声检测

颈部超声由经验丰富的医师进行专业操作, 双侧颈总动脉CIMT平均值取距离颈总动脉分叉处远端1 cm处的内膜内表面到中膜外表面的垂直距离, 分别对左右颈总动脉测量3次, 取平均值。颈

动脉内膜增厚时CIMT \geq 0.08 cm。

1.3 实验室检测指标及方法

所有患者隔夜空腹10 h以上后,用真空采血管抽取肘静脉血,离心分离血清并保存于-80℃备用。采用ELISA法,按照各自检验试剂盒说明书检测血清中白介素6(IL-6)、C反应蛋白(C-reactive protein, CRP)、丙二醛(malondialdehyde, MDA)及超氧化物歧化酶(superoxide dismutase, SOD)水平;循环酶法检测血浆中同型半胱氨酸(HCY)。采用酶法检测血清中总胆固醇(TC)、三酰甘油(TG);全自动生化分析仪测定载脂蛋白ApoA1, ApoB以及丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶(AST)、 γ -谷氨酰转肽酶;直接法检测血清中高密度脂蛋白胆固醇(high-density lipoprotein, HDL);Friedewald公式计算法检测血清低密度脂蛋白胆固醇(low-density lipoprotein, LDL);葡萄糖氧化酶法用于测定血糖(glucose, GLU)水平。体重指数(BMI)=体重/身高²。

1.4 统计学处理

采用SPSS16.0软件进行统计分析,计量资料以均数 \pm 标准差($\bar{x}\pm s$)表示,多组间采用单因素方差分析(ANOVA),两组间采用 t 检验;计数资料结果以例数(%)表示,采用卡方检验;相关性分析采用Spearman。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组患者的基础指标比较

四组患者的年龄、饮酒年限、LDL、HDL及GLU之间的差异均无统计学意义(均 $P>0.05$)。A, B两组间BMI, TG, AST以及 γ -GT差异均无统计学意义($P>0.05$),但均显著高于C, D两组,差异有统计学意义($P<0.05$)。CIMT, TC, ApoA1, ApoB及ALT分别在A, B两组间和C, D两组间差异均无统计学意义(均 $P>0.05$);但A, B两组均显著高于D组,差异有统计学意义($P<0.05$, 表1)。

表1 各组患者的基础指标

Table 1 Basic indicators of patients in each group

指标	A组(n=60)	B组(n=54)	C组(n=20)	D组(n=34)
年龄/岁	46.89 \pm 6.78	47.15 \pm 6.81	46.94 \pm 6.75	48.02 \pm 6.84
饮酒时间/年	22.35 \pm 7.82	23.09 \pm 7.94	22.65 \pm 7.87	23.58 \pm 8.13
BMI/(kg·m ⁻²)	26.93 \pm 2.71* [#]	26.42 \pm 2.65* [#]	24.28 \pm 2.39	23.97 \pm 2.36
CIMT/mm	0.092 \pm 0.013 [#]	0.09 \pm 0.011 [#]	0.079 \pm 0.015	0.07 \pm 0.009
血脂/(mmol·L ⁻¹)				
TC	5.64 \pm 0.96 [#]	5.53 \pm 0.92 [#]	5.25 \pm 0.71	4.85 \pm 0.73
TG	2.45 \pm 1.79* [#]	2.34 \pm 1.43* [#]	1.39 \pm 0.62	1.13 \pm 0.51
LDL	3.31 \pm 0.82	3.26 \pm 0.74	3.07 \pm 0.69	2.99 \pm 0.62
HDL	1.35 \pm 0.2	1.32 \pm 0.17	1.28 \pm 0.13	1.31 \pm 0.16
载脂蛋白/(g·L ⁻¹)				
ApoA1	1.45 \pm 0.34 [#]	1.56 \pm 0.43 [#]	1.39 \pm 0.37	1.28 \pm 0.31
ApoB	1.17 \pm 0.25 [#]	1.15 \pm 0.23 [#]	1.09 \pm 0.21	0.99 \pm 0.18
GLU/(mmol·L ⁻¹)	5.88 \pm 0.76	5.83 \pm 0.74	5.72 \pm 0.68	5.69 \pm 0.7
肝功能指标/(U·L ⁻¹)				
ALT	32.57 \pm 15.83 [#]	33.24 \pm 16.05 [#]	28.16 \pm 10.28	23.95 \pm 9.74
AST	31.98 \pm 16.45* [#]	31.42 \pm 15.74* [#]	23.67 \pm 8.31	22.89 \pm 7.97
γ -GT	50.45 \pm 28.16* [#]	53.73 \pm 29.58* [#]	31.04 \pm 15.27	28.56 \pm 12.71

与C组相比, * $P<0.05$; 与D组相比, [#] $P<0.05$ 。

Compared with group C, * $P<0.05$; compared with group D, [#] $P<0.05$.

2.2 各组患者颈动脉内膜增厚发生率

A组CIMT增厚率显著高于其余3组($P<0.05$); B, C两组间CIMT增厚率均高于D组, 但差异无统计学意义($P>0.05$, 表2)。

2.3 各组患者炎症和氧化应激因子水平比较

A组IL-6水平显著高于C, D两组($P<0.05$), B组显著高于D组($P<0.05$)。CRP在A, B, C 3组间的差异无统计学意义, 但均显著高于D组($P<0.05$)。HCY在四组间差异无统计学意义($P<0.05$)。A组、B组MDA水平显著低于D组($P<0.05$)。A, B, C 3组中SOD显著低于D组($P<0.05$, 表3)。

2.4 AFLD 合并 Hp 感染 CIMT 与基础指标的相关性

AFLD合并Hp感染组CIMT与年龄, BMI, TC, TG均呈显著正相关(年龄: $r=0.893$, $P<0.0001$; BMI: $r=0.895$, $P<0.0001$; TC: $r=0.590$, $P<0.0001$; TG: $r=0.554$, $P<0.0001$; 图1)。

2.5 AFLD 合并 Hp 感染 CIMT 与炎症和氧化应激因子的相关性

AFLD合并Hp感染组CIMT与IL-6, CRP呈正相关(IL-6: $r=0.629$, $P<0.0001$; CRP: $r=0.806$, $P<0.0001$); CIMT与MDA, SOD呈负相关(MDA: $r=-0.523$, $P<0.0001$; SOD: $r=-0.698$, $P<0.0001$; 图2)。

表2 各组患者颈动脉内膜增厚发生率

Table 2 Incidence of carotid artery intimal thickening in each group

组别	<i>n</i>	增厚/例	正常/例	增厚率/%
A组	60	41	19	68.33
B组	54	27	27	50.00
C组	20	9	11	45.00
D组	34	10	24	29.41
χ^2			13.835	
<i>P</i>			0.003	

表3 各组患者的炎症和氧化应激因子水平

Table 3 Levels of inflammatory and oxidative stress factors in each group

组别	<i>n</i>	IL-6/(ng·L ⁻¹)	CRP/(mg·dL ⁻¹)	HCY/(μmol·L ⁻¹)	MD*/(ng·L ⁻¹)	SOD/(ng·L ⁻¹)
A组	60	19.24 ± 11.07 ^{*#}	3.96 ± 1.74 [#]	38.64 ± 9.21	5.68 ± 3.73 [#]	62.13 ± 54.07 [#]
B组	54	16.31 ± 8.96 [#]	3.81 ± 1.49 [#]	37.93 ± 8.95	7.17 ± 5.34 [#]	65.36 ± 53.79 [#]
C组	20	14.19 ± 6.78	4.37 ± 2.28 [#]	35.78 ± 7.16	7.21 ± 5.40	58.74 ± 52.32 [#]
D组	34	12.45 ± 4.82	2.92 ± 1.13	34.89 ± 7.32	11.08 ± 9.56	108.42 ± 97.61

与C组相比, $*P<0.05$; 与D组相比, $^{\#}P<0.05$ 。

Compared with group C, $*P<0.05$; compared with group D, $^{\#}P<0.05$.

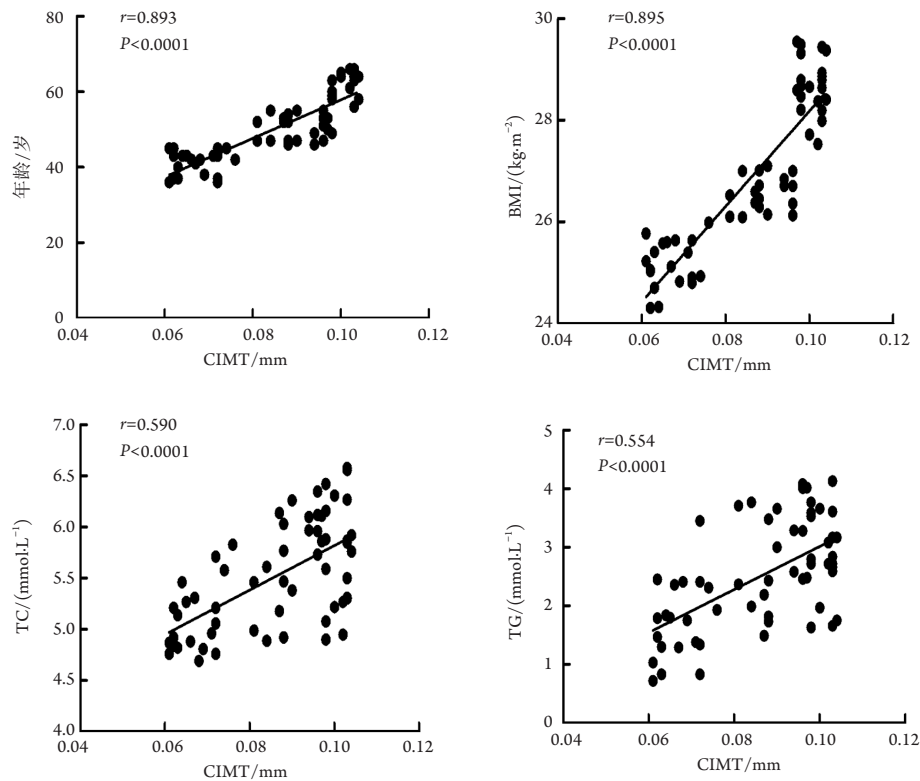


图1 AFLD合并Hp感染CIMT与基础指标的相关性分析

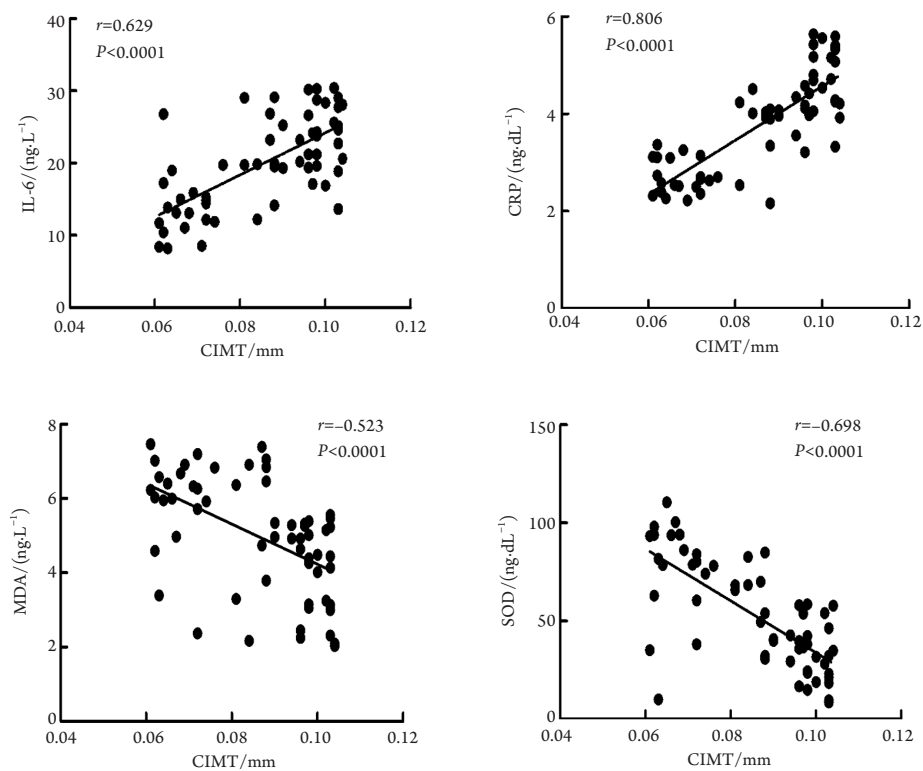
Figure 1 Correlation analysis of CIMT and basic indicators in alcoholic fatty liver disease complicated with *Hp* infection

图2 AFLD合并Hp感染CIMT与炎症和氧化应激因子的相关性分析

Figure 2 Correlation analysis of inflammatory and oxidative stress factors in alcoholic fatty liver with *Hp* infection CIMT

3 讨论

AS的临床特点为动脉管壁硬化增厚, 弹性随之减弱, 管腔亦缩小^[7]。近年来, 在评价早期动脉粥样硬化的指标中, CIMT已被国内外专家学者广泛认可。早期研究^[8]发现: 在AS的过程伴随着平滑肌细胞向血管内膜的迁移增殖、炎性细胞浸润、脂质过氧化物损伤等炎症和氧化应激反应, 故有学者^[9]认为AS是一种炎症性疾病。其发病机制尚未有全面阐释, 目前仍存在平滑肌突变、脂质浸润及炎症等多种学说^[10]。NAFLD已被证实是AS发生的关键因素, 此外, 脂肪性肝病还包括AFLD^[11]。乙醇及其代谢物在体内会因营养障碍、缺氧及炎性因子对肝细胞造成损伤, 引起肝脂肪变性、炎症及纤维化, 最终导致肝硬化。乙醇代谢降低了乙醇脱氢酶、细胞色素P450的合成, 进而使NADH减少, 加速合成脂肪酸并促进脂肪变性, 加上代谢产物乙醛对细胞器的损伤, 使细胞内氧化应激反应进一步加重^[12-13]。此外, 乙醇通过激活枯否氏细胞及巨噬细胞诱导IL-6、肿瘤坏死因子(tumor necrosis factor, TNF- α)等炎症免疫因子的分泌, 产生氧自由基并氧化胞内物质, 加重肝细胞损伤, 使肝转运脂肪能力下降^[14]。Hp首先在胃黏膜活检组织中分离得到, 目前全世界约50%的人口被感染, 以往研究^[15]发现机体感染后能将细胞毒素相关蛋白(Cag A)及空泡细胞毒素(Vac A)释放出来, 对胃黏膜造成损伤, 并导致胃炎、胃溃疡。随着科研水平的提高, 有报道^[16]称Hp慢性感染及其产生的毒素可导致AS的发生, 且Cag A呈阳性的慢性感染与CIMT甚至脑梗死密切相关。有学者^[17-18]认为: Hp感染人群CIMT仅与年龄有关, 而与Hp感染无关。因此Hp感染与AS的关系尚有一定争议。

本研究发现: A, B两组BMI, TG, AST以及 γ -GT均显著高于C, D两组($P < 0.05$); CIMT, TC, ApoA1, ApoB及ALT分别在A, B两组间和C, D两组间差异无统计学意义($P > 0.05$), 但A、B两组均显著高于D组($P < 0.05$)。A组病例CIMT增厚率显著高于其余引起组($P < 0.05$)。该统计结果表明AFLD合并Hp感染者CIMT显著增厚且发生率提高, BMI、血脂及肝功能指标水平明显增加, 推测AFLD合并Hp感染首先使机体ApoA1, ApoB及TC, TG等升高, 血脂代谢发生紊乱, 肝受损后将肝细胞内的酶类ALT, AST等释放入血, 因而血清中ALT和AST水平升高, 且升高程度与肝细胞损伤程度保存一致。同时肝功能受损可引起肝

内梗阻, 使存在于肝细胞质及胆管上皮中的 γ -GT排泄受阻, 并随胆汁返流入血中, 最终血清中谷氨酰转氨酶升高。长期肝功能异常进一步加重脂质代谢的紊乱程度, BMI显著升高^[19]。此外, A组IL-6, CRP水平均显著高于D组($P < 0.05$); 与D组相比, B, C两组均有不同程度的升高。研究^[20]发现: 肝细胞由脂肪变性逐步向脂肪性肝炎、肝纤维化甚至肝硬化进展的过程中, 伴随着炎症和氧化应激反应, 血浆中的相关指标显著升高。Hp感染后可通过结合内皮细胞并刺激其分泌IL-6, CRP等炎症因子, 这些炎症因子于动脉壁内沉积而使血管内皮损伤, CRP还能结合脂蛋白, 将补体系统激活, 进而产生更多炎症介质并释放氧自由基, 促进AS的发生和进展^[21]。SOD可通过清除超氧化物以使细胞免受氧化损伤, 其活力高低可作为机体清除氧自由基的能力的间接反映^[22-23]。已有研究^[24]证实: Hp感染后, 机体氧化因子显著升高, 抗氧化因子水平降低。本研究结果显示: A, B两组MDA水平显著低于D组($P < 0.05$); A, B, C三组SOD水平显著低于D组($P < 0.05$)。推测Hp感染、AFLD及二者合并症导致了患者机体氧化和抗氧化能力失衡, 或因纠正其平衡而重新启动氧化应激反应, 最终仍可加速动脉粥样硬化的进展。本研究分析了AFLD合并Hp感染患者CIMT与各指标的相关性, 发现CIMT与年龄, BMI, TC, TG, IL-6, CRP均呈显著正相关($P < 0.05$), 与MDA, SOD呈负相关($P < 0.05$)。该结果说明年龄、血脂、炎症因子及氧化应激因子对AFLD合并Hp感染患者CIMT有不同程度的影响。

综上, AFLD合并Hp感染患者CIMT与年龄、BMI、血脂、炎症及氧化应激因子均有显著相关性, 且相关程度可能跟疾病所处的不阶段有关系, 但有待进一步加大样本量及细化病理进展阶段以获取更加准确的结论。

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