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血清 CD5L 对肝脏疾病患者的临床意义研究 *

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摘要 目的：检测 CD5L 水平在肝脏疾病患者血清中的变化，并分析其临床意义。**方法：**采用 ELISA 法检测 41 例慢性肝炎患者、192 例肝硬化患者、69 例肝癌患者和 136 例健康对照血清 CD5L 水平。全自动生化分析仪测定肝功能指标，Spearman 相关性分析用于评估 CD5L 与肝功能指标的关系。受试者工作曲线（receiver operator characteristic, ROC）分析血清 CD5L 的潜在诊断价值。**结果：**与健康对照相比，CD5L 水平在肝炎、肝硬化、肝癌患者中显著降低（$P<0.01$）。肝硬化患者血清 CD5L 水平较肝炎及肝癌患者显著降低（$P<0.01$）。肝硬化代偿期和失代偿期患者血清 CD5L 水平无显著差异。血清 CD5L 水平与 FIB-4 指数(肝纤维化评分)呈显著负相关（r=-0.2688，P=0.0001）。Spearman 相关性分析结果显示：在肝炎患者中，血清 CD5L 与总胆红素（T-BIL）、直接胆红素（D-BIL）、间接胆红素（I-BIL）显著正相关；在肝硬化患者中，CD5L 与其他肝功指标无显著相关性；在肝癌患者中，CD5L 与碱性磷酸酶（ALP）显著正相关。以健康人为对照组，肝硬化患者为病例组，ROC 分析显示血清 CD5L 的诊断特异性为 85.3%，敏感性为 77.1%。**结论：**CD5L 水平在肝炎、肝硬化及肝癌患者血清中显著降低，且在肝硬化患者中最低。CD5L 水平与肝纤维化评分 FIB-4 指数负相关，可作为监测肝纤维化进展的潜在生物标志物。

关键词：CD5L；肝纤维化；肝病；诊断

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Clinical Significance of Serum CD5L in Patients with Liver Disease*

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ABSTRACT Objective: To detect the CD5L levels in serum from patients with liver disease and to explore its protential clinical significance. **Methods:** 41 patients with chronic hepatitis, 192 patients with liver cirrhosis, 69 patients with liver cancer and 136 healthy controls were included in this study. Serum CD5L levels were detected by ELISA assay. Automatic biochemical analyzer was used to measure liver function indexes. Spearman correlation analysis was used to evaluate the relationship between serum CD5L levels and liver function indexes. Receiver operator characteristic (ROC) curve analysis was used to evaluate the potential diagnostic value of serum CD5L levels. **Results:** Compared with healthy controls, CD5L levels were significant decreased in patients with hepatitis, cirrhosis and hepatocellular carcinoma ($P<0.01$). The serum CD5L levels in patients with cirrhosis was significant lower than that in patients with hepatitis or hepatocellular carcinoma ($P<0.01$). There was no significant difference for serum CD5L level between patients with decompensated liver cirrhosis and compensatory liver cirrhosis. Serum CD5L level was negatively correlated with FIB-4 index (r=-0.2688, P=0.0001). Spearman correlation analysis showed that there was a significant positive correlation between serum CD5L with total bilirubin (T-BIL), direct bilirubin (D-BIL) and indirect bilirubin (I-BIL) in hepatitis patients. There was no significant correlation between CD5L and other liver function indexes in patients with cirrhosis. CD5L was significant positively correlated with alkaline phosphatase (ALP) in patients with liver cancer. The ROC analysis showed that the diagnostic specificity and sensitivity of serum CD5L were 85.3% and 77.1%. **Conclusions:** CD5L levels were significant decreased in serum form patients with liver injury, and were the lowest in patients with cirrhosis. CD5L might be a potential biomarker for monitoring liver fibrosis progression.

Key words: CD5L; Liver fibrosis; Liver disease; Diagnosis

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前言

肝纤维化是多种损伤因子持续作用下的创面愈合反应[1]，肝纤维化主要特征是肝组织损伤和异常修复、肝星状细胞增生活化、及细胞外基质（extracellular matrix，ECM）过度沉积[2,3]。肝纤维化持续进展最终可导致肝癌甚至肝衰竭，因此评估肝纤维化进展在临床实践中至关重要。目前，一些生物标志物已经被用来评估肝纤维化的严重程度，如透明质酸（hyaluronic acid，

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HA），Ⅲ型前胶原氨基末端肽（N-terminal procollagen peptide Ⅲ，PCⅢNP），Ⅳ型胶原（Type IV collagen，C-Ⅳ）和层粘连蛋白（Laminin，LN）。此外，天冬氨酸转氨酶 / 血小板比值指数（APRI）或纤维化 -4（Aspartate aminotransferase-to-Platelet Ratio Index，FIB-4）也是一种无创肝纤维化标志物[1,4-6]。

CD5 抗原样蛋白（CD5 molecule-like，CD5L），又称为巨噬细胞凋亡抑制分子，属于富含半胱氨酸清道夫受体超家族[7]，主要由淋巴细胞和巨噬细胞表达[8,9]。CD5L 作为脂质合成的关键调节分子，在调节炎症反应过程中发挥重要作用[10,11]。近年研究显示，CD5L 是多种疾病的潜在标志物。如 CD5L 对区分细菌感染和病毒感染肺炎中具有潜在应用价值[12]，也可作为糖尿病肾衰竭[13]和脓毒症[14]预后监测的生物标志物，还可以用于预测创伤患者急性肺实质损伤和急性呼吸窘迫综合征 [15]。然而，CD5L 在肝脏疾病中的作用研究较少。本研究通过检测肝纤维化不同进展期（肝炎、肝硬化和肝癌患者）血清 CD5L 水平差异，以评估 CD5L 对肝脏疾病患者的临床意义。

1 材料与方法

1.1 患者血清样本

本研究招募了 2020 年 1 月至 2021 年 3 月在唐都医院收治的 302 例不同程度肝病患者，包括慢性肝炎（n=41）、肝硬化患者（n=192）和肝细胞癌患者（n=69）。根据 FIB-4 评分[16]将肝患者分为：F0-1（无或轻度纤维化）：FIB-4 值 <1.45，F2（中度纤维化）：1.45<FIB-4 值 <3.25，F3-4（重度纤维化）：FIB-4 值 >3.25。对照组为 136 例健康人。FIB-4 计算方法：年龄（岁）×AST（U/L）/ 血小板计数（10^9/L）×ALT（U/L）的平方根。所有血液样本按照血液采集和处理的标准程序采集。该研究经空军军医大学唐都医院伦理委员会批准。

1.2 血清生物标志物检测

肝功能指标包括总蛋白（TP）、白蛋白（ALB）、球蛋白（GLO）、白蛋白 / 球蛋白（A/G）、总胆红素（T-BIL）、直接胆红素（D-BIL）、间接胆红素（I-BIL）、谷丙转氨酶（ALT）、天冬氨酸转氨酶（AST）、碱性磷酸酶（ALP）和总胆汁酸（TBA）。均采用全自动生化分析仪测定（Beckman Coulter，AU5800，Germany）。PLT 采用血细胞分析仪检测（SysmexXN-9000，Japan）。

1.3 血清 CD5L 水平检测

采用 ELISA 试剂盒（Cloud-Clone Crop.，Lot: L201023822，武汉，中国）检测血清 CD5L 浓度。按照操作说明书进行：血清用 PBS 稀释 100 倍后加入板中，37℃孵育 1 h；第二，每孔加入 100 μL 兔抗人 CD5L 抗体，37℃孵育 1 h；第三，每孔加入 100 μL 辣根过氧化物酶（HRP）标记山羊抗兔二抗，37℃孵育 30 min；然后每孔加入 90 μL TMB，37℃孵育 10-20 min；最后加入 50 μL 终止液，测量 450 nm 处吸光度。

1.4 统计分析

所有定量数据用中位数（四分位区间：Q75-Q25）表示。多组统计评价采用 Kruskal-Wallis 检验，两组统计评价采用 Mann-Whitney 检验。采用 Spearman 秩相关检验分析 CD5L 与其他临床指标的相关性。统计分析均采用 IBM Statistic SPSS v. 21.0 或 Graphpad prism 8.0 进行。利用 R 软件（版本 4.1.3）做相关性矩阵图。P<0.05 为差异具有统计学意义。

2 结果

2.1 研究对象肝功信息

136 健康对照、41 例慢性肝炎、192 例肝硬化患者和 69 例肝细胞癌患者的肝功信息见表 1。结果显示：与健康对照相比，肝病患者血清 TP、ALB、A/G、PLT 和 INR 水平显著降低（P<0.0001），T-BIL、D-BIL、I-BIL、ALT、AST、AST/ALT、ALP、TBA 和 GLO 水平均显著升高（P<0.01）。

表 1 血清样本的肝功信息

Table 1 Liver function information from serum samples

	healthy(n=136)	hepatitis(n=41)	cirrhosis(n=192)	HCC(n=69)	*P*-value
TP(g/L)	71.05 (73.8-68.8)	62.4 (68.25-57.85)	60.15 (66.03-53.3)	62.8 (70.5-57.1)	<0.0001
ALB(g/L)	47 (47.5-45.4)	35.7 (41.15-31.4)	31.95 (36.88-27.78)	33.7 (37.4-30.9)	<0.0001
GLO(g/L)	24.3 (26.88-22.4)	25.2 (30.65-20.8)	25.7 (31.78-22)	28.4 (34.7-23)	0.0024
A/G	1.9 (2.1-1.7)	1.5 (1.7-1.1)	1.3 (1.6-0.98)	1.2 (1.6-1)	<0.0001
T-BIL (U mol/L)	14.25 (16.95-12.43)	83.7 (216.3-25.9)	31.75 (64.9-18.7)	30.7 (55.3-23.1)	<0.0001
D-BIL (U mol/L)	3.9 (4.9-3.2)	52.9 (117.85-9.8)	13.15 (26.38-8.1)	13.5 (24.3-9.5)	<0.0001
I-BIL (U mol/L)	10.3 (12.18-9)	32.5 (94.05-15.3)	18.65 (34.1-10.5)	17.5 (30.1-13.3)	<0.0001
ALT(U/L)	16 (21-12)	130 (359-72.5)	28.5 (48-18)	31 (51-19)	<0.0001
AST(U/L)	19.5 (22-17)	99 (219-48)	36.5 (55.25-26.75)	56 (108-37)	<0.0001
AST/ALT	1.24 (1.47-1)	0.73 (1.09-0.59)	1.37 (1.7-0.98)	1.62 (3.24-1.21)	<0.0001
ALP(U/L)	60 (73-53)	110 (145-78)	93 (129-71)	102 (192-85.5)	<0.0001
TBA (U mol/L)	2.7 (4.35-1.8)	103.85 (344.48-15.65)	34.5 (119.2-9.3)	25.8 (87-6.7)	<0.0001
PLT (10^9/L)	230.5 (271-198)	167 (218.25-116)	65.5 (103.25-43.75)	93 (135.75-67)	<0.0001
INR	29.7 (30.6-22.7)	1.04 (1.32-0.95)	1.21 (1.42-1.07)	1.09 (1.23.-1.01)	<0.0001

2.2 CD5L 水平在肝硬化患者血清中降低

血清 CD5L 水平在肝炎、肝硬化、肝癌患者及健康对照组中分别为:89.65 (304.6-52.65)、55.19(110.03-31.29)、112.22(306.87-46.02)及 208.85(326.72-141.22)ng/mL。与健康对照相比,肝病患者血清 CD5L 水平显著降低(图 1A)。在不同肝病患者中,与肝炎和肝癌患者相比,肝硬化患者的血清 CD5L 水平最低(P<0.01)。肝硬化代偿期和失代偿期患者血清 CD5L 水平无显著差异(图 1B,P=0.7355)。

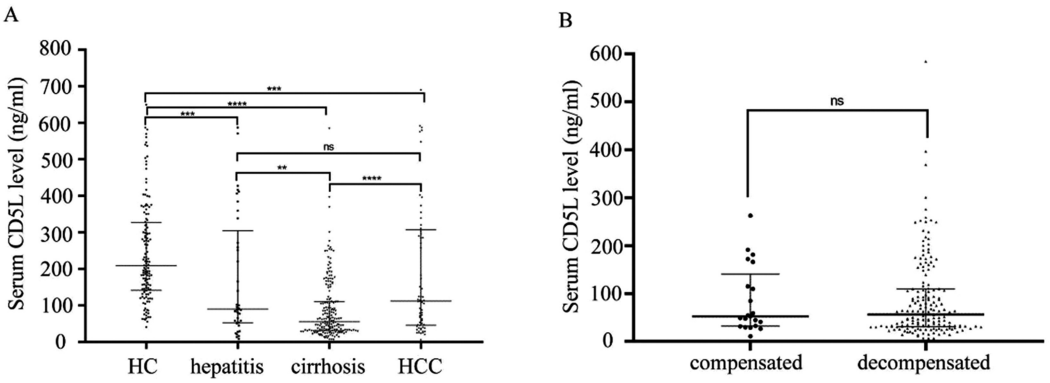

图 1 肝病患者血清 CD5L 水平

Fig.1 Serum CD5L levels in patients with liver disease

Note: A. Serum CD5L levels in healthy, hepatitis, cirrhosis and hepatocellular carcinoma patients; B. Serum CD5L levels in patients with compensatory and decompensated cirrhosis. **, P<0.01; ***, P<0.001; ****, P<0.0001; ns, P>0.05.

2.3 血清 CD5L 水平与肝纤维化分期的关系

FIB-4 指数是反映肝炎及肝硬化患者肝纤维化程度的一项评分,Spearman 相关分析显示, 血清 CD5L 与 FIB-4 指数呈显著负相关(r=-0.2688,P=0.0001;图 2A)。根据 FIB-4 评分,将肝炎和肝硬化患者分为三组:F0-1 (FIB-4: <1.45;n=22),F2 (FIB-4: 1.45-3.25;n=65)和 F3-4 (FIB-4≥3.25;n=146),三组患者的血清 CD5L 水平依次降低, 分别为:95.85 (270.98 ~ 60.97)、84.39 (220.84 ~ 44.93)、50.38 (106.45 ~ 30.01)ng/mL(图 2B)。

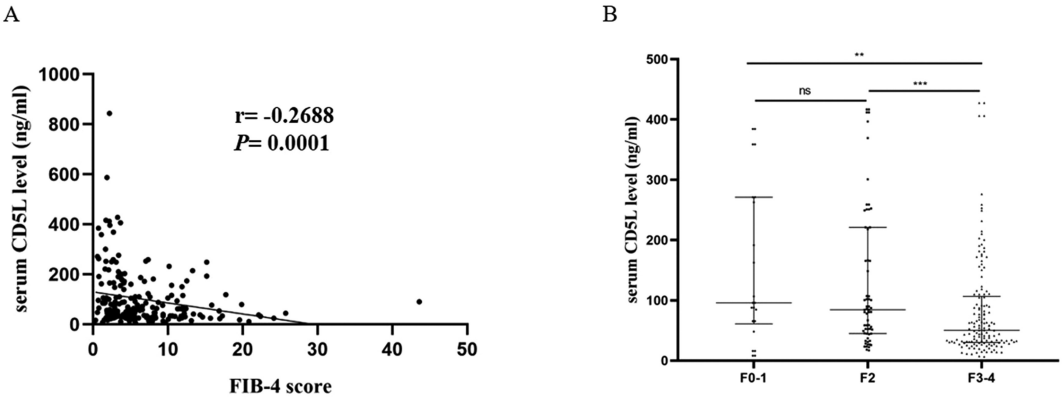

图 2 血清 CD5L 水平与肝纤维化进展的关系

Fig. 2 Relationship between serum CD5L level and progression of liver fibrosis

Note: A. Correlation between serum CD5L level and FIB-4 score. B. The serum CD5L level was determined by FIB-4 score. **, P<0.05; ***, P<0.0001 .

2.4 CD5L 与肝功能指标的相关性分析

首先,分析了 302 例肝病患者(包括肝炎、肝硬化、肝癌)血清 CD5L 与肝功指标的相关性。如图 3A 显示,血清 CD5L 水平与 AST(r=0.13,P=0.04)、ALP (r=0.12, P=0.03)显著相关。其次,分别分析了肝炎、肝硬化和肝癌患者中血清 CD5L 水平与肝功能指标的相关性。结果显示, 肝炎患者血清 CD5L 与 T-BIL (r=0.40,P=0.01)、D-BIL (r=0.42,P=0.01)、I-BIL (r=0.40, P=0.01)呈显著正相关(图 3B)。肝硬化患者血清 CD5L 水平与肝功能指标无显著相关性(图 3C)。在肝癌患者中,血清 CD5L 与 ALP 显著相关(r=0.27,P=0.03)(图 3D)。此外,肝癌患者血清 CD5L 与肿瘤标志物的相关性分析显示,CD5L 与 CEA (r=0.031,P=0.866)、AFP (r=0.323,P=0.067)无显著相关性。

2.5 血清 CD5L 对肝病的潜在诊断价值

以健康人作为对照组,肝炎及肝硬化患者作为病例组,ROC 曲线分析显示, 血清 CD5L 水平的最佳临界值为 110 ng/mL,诊断特异性和敏感性分别为 86.8%和 73.0%(图 4A)。以健康人作为对照组,肝硬化患者作为病例组,ROC 分析显示,血清 CD5L 的诊断特异性和敏感性分别为 85.3%和 77.1%(图 4B);以健康人作为对照组, 肝炎患者作为病例组,ROC 分析显示, 血清 CD5L 的诊断特异性和敏感性分别为 88.2%和 61%(图 4B)。

3 讨论

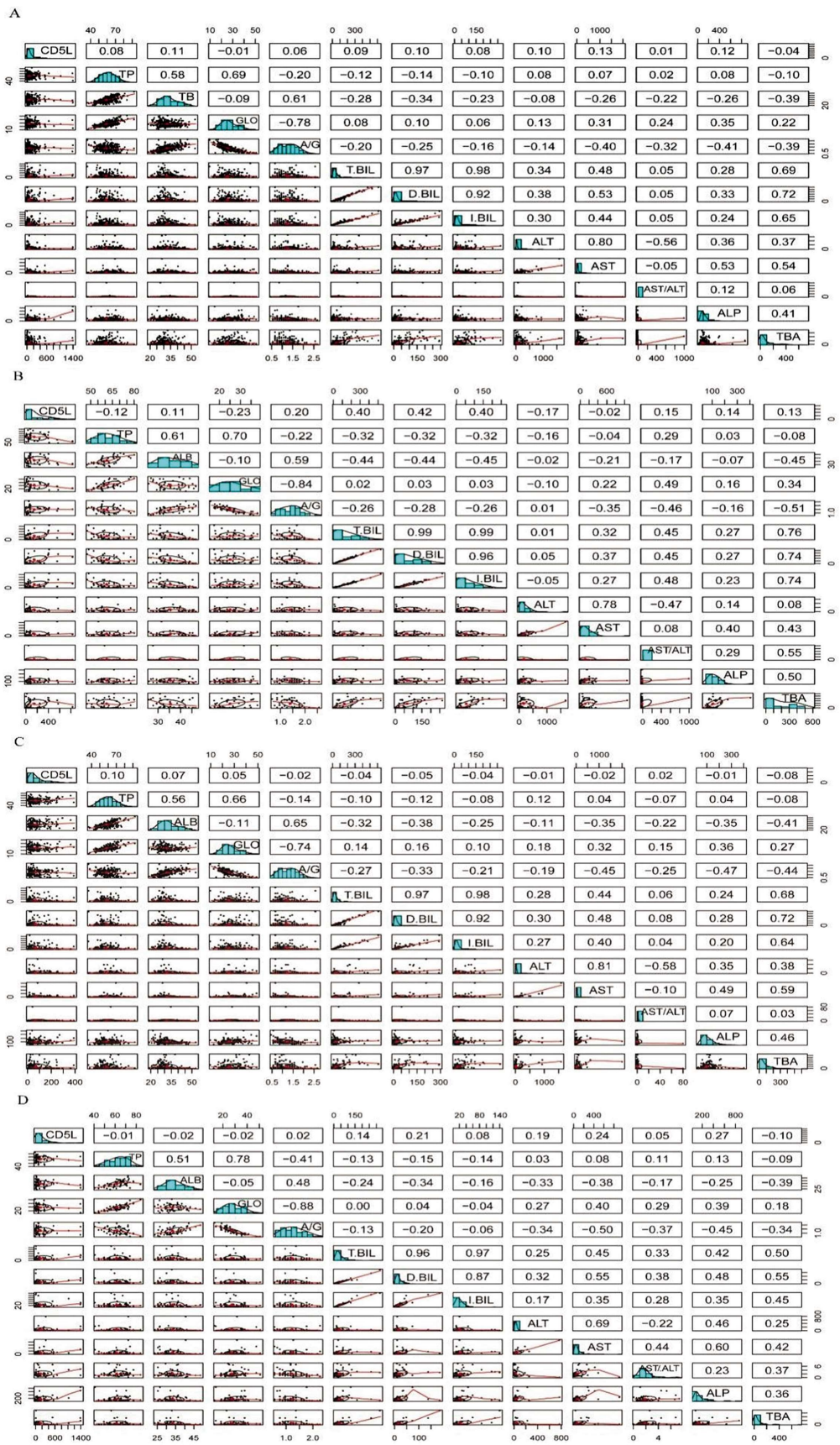

图 3 血清 CD5L 水平与肝功能指标的相关性分析

Fig. 3 Correlation analysis of serum CD5L level and liver function index

Note: A: Correlation between serum CD5L levels and liver function indices in all patients with liver disease, hepatitis cirrhosis and hepatocellular carcinoma; B: Correlation between serum CD5L level and liver function index in patients with hepatitis;

C: Correlation between serum CD5L level and liver function index in patients with cirrhosis;

D: Correlation between serum CD5L level and liver function index in patients with hepatocellular carcinoma.

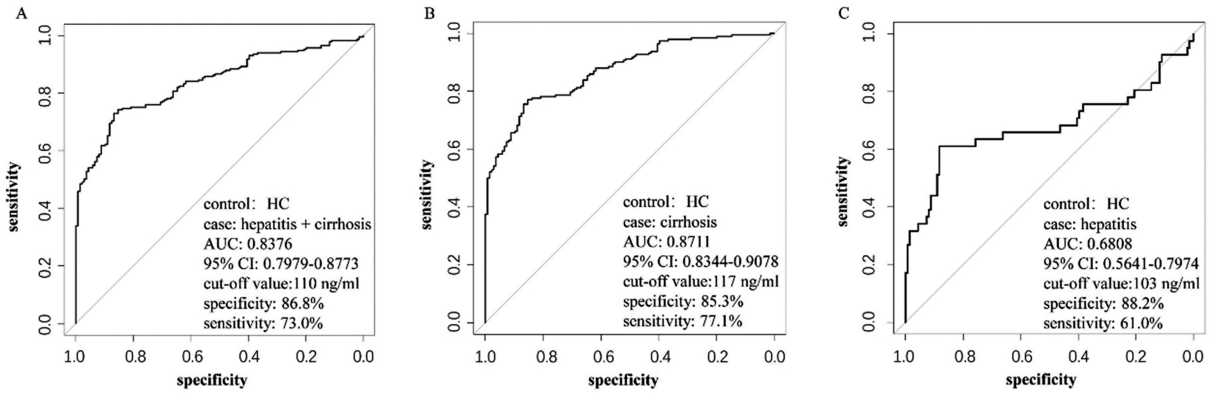

图 4 肝病患者血清 CD5L 水平的 ROC 曲线分析

Fig. 4 ROC curve analysis of serum CD5L level in patients with liver disease

Note: A: ROC curves of hepatitis or cirrhosis patients were obtained in the control group and the case group.

B: The ROC curves of the control group were healthy persons and the case group were cirrhotic patients.

C: The ROC curves of the control group were healthy persons and the case group was hepatitis patients.

CD5L 是一种富含半胱氨酸的可溶性清道夫受体，在脂质代谢和免疫调节中发挥重要作用[8,17]。一般认为 CD5L 主要由巨噬细胞表达[8,9,18]，Aran 等[19]发现 CD5L 在肝细胞中也有表达。近年来，对 CD5L 的研究主要集中在感染性疾病[14,20]、心脏病[21,22]、肺病[12,23]、甲状腺疾病[24]和自身免疫性疾病，如类风湿性关节炎[25]和系统性红斑狼疮[26]等。但对肝脏疾病尤其是肝纤维化的研究较少。

本研究发现肝病患者血清 CD5L 水平显著降低，并且，与肝炎和肝癌患者相比，肝硬化患者血清 CD5L 水平最低。其原因可能是：肝硬化坏死组织被假小叶取代，形成瘢痕组织，炎性活动程度较低。此外，肝硬化组织中的免疫细胞浸润程度较肝癌患者低，因此，可能导致免疫细胞分泌的 CD5L 水平在肝硬化患者中低于肝癌患者。ROC 分析显示，血清 CD5L 对肝硬化患者具有一定的诊断价值。此外，血清 CD5L 水平与肝纤维化程度呈显著负相关，提示血清 CD5L 检测可能有助于监测肝纤维化的进展。Spearman 相关分析显示，肝炎患者血清 CD5L 水平与一些肝功能指标(T-BIL、D-BIL、I-BIL)有显著相关性，而肝硬化患者血清 CD5L 与肝功能指标无显著相关性，提示CD5L 可能是肝病患者中独立的辅助诊断指标。Maehara N 等[27]研究显示 CD5L 对肝癌发生发展过程具有一定的抑制作用。Yunxiu Luo[28]等研究发现，CD5L 与肝癌患者存活率提高相关，可作为肝癌患者预后标志物。Bárcena [29]等研究显示肝表面 CD5L 的积累可通过抑制 TGF-β 信号和免疫细胞浸润，从而抑制慢性肝损伤。本研究发现肝癌患者血清 CD5L 水平明显下降，提示 CD5L 可能在肝癌发生发展过程中具有保护作用。

然而，Gangadharan [30]，Mera[31]和等人的研究报道 HCV 感染患者血清 CD5L 水平显著高于健康对照组，这与本文结果矛盾。本文与上述研究的差别在于，本文研究的患者主要是乙型肝炎病毒感染，而 Gangadharan 和 Mera 的研究主要是丙型肝炎病毒感染的患者；其次，本文研究的大多数患者都有过两次或两次以上的住院经历，并接受过药物干预。因此，肝硬化患者血清 CD5L 水平变化的不一致性有待进一步验证。

本文的不足在于，由于缺乏初诊患者，故未分析药物治疗对血清 CD5L 水平的影响。值得注意的是，虽然本研究所纳入的肝纤维化患者的进展阶段不同，但所用药物性质基本相同，均为保肝抗黄药。因此，各组药物的影响理论上一致。但在肝纤维化的不同阶段，药物治疗前后血清 CD5L 水平是否存在差异仍需进一步研究。综上所述，本文研究显示肝硬化患者血清 CD5L 水平降低，且与肝纤维化程度呈负相关，CD5L 可作为监测肝纤维化进展的生物标志物。

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