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血清球蛋白/胆碱酯酶(G/C)及 VEGF 在不同病情严重程度肝硬化门脉高压性胃病患者中的表达差异及其疾病诊断价值分析 *

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摘要 目的:探讨血清球蛋白/胆碱酯酶(G/C)及血管内皮细胞生长因子(VEGF)在不同病情严重程度肝硬化门脉高压性胃病患者中的表达差异及其疾病诊断价值。**方法:**选取我院 2020 年 12 月到 2023 年 12 月收治的 80 例肝硬化门脉高压性胃病患者作为研究对象,依照患者肝硬化门脉高压性胃病严重程度进行分组,分为轻度组(n=45)及重度组(n=35),另选取同期收治的肝硬化门脉高压未合并胃病的 40 例患者作为对照组。对比三组患者临床资料及 G/C、VEGF 表达水平,采取 logistics 回归模型分析肝硬化门脉高压性胃病的独立影响因素,并采用 Pearson 检验分析 G/C、VEGF 与不同病情严重程度肝硬化门脉高压性胃病的相关性,最后建立受试者工作特征(ROC)曲线分析 G/C、VEGF 对肝硬化门脉高压性胃病的诊断价值。**结果:**三组患者性别、年龄、合并基础疾病、病因、Child-Pugh 分级、AST、ALT 水平对比无明显差异($P>0.05$),肝硬化病程、Hb、PLT、Alb、G/C、VEGF 水平对比差异显著($P<0.05$);G/C 升高、VEGF 降低为肝硬化门脉高压性胃病的独立影响因素($P<0.05$);G/C(r=0.493)、VEGF(r=-0.542)的表达均与肝硬化门脉高压性胃病严重程度密切相关($P<0.05$);VEGF 对肝硬化门脉高压性胃病的诊断曲线下面积为 0.822,最佳诊断界限值为 143.45 ng/mL。G/C 对肝硬化门脉高压性胃病的诊断曲线下面积为 0.875,最佳诊断界限值为 0.87。两者联合的曲线下面积为 0.932。G/C 联合 VEGF 对肝硬化门脉高压性胃病的诊断灵敏度与特异度明显高于单一指标($P<0.05$)。**结论:**G/C、VEGF 为肝硬化门脉高压性胃病的独立影响因素,且与不同病情严重程度具有显著关系,两者联合可提升度肝硬化门脉高压性胃病的诊断效能。

关键词:血清球蛋白/胆碱酯酶;血管内皮细胞生长因子;肝硬化门脉高压性胃病;肝硬化;诊断价值

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Differential Expression and Diagnostic Value of Serum Globulin/Cholinesterase (G/C) and VEGF in Patients with Different Severity of Liver Cirrhosis and Portal Hypertensive Gastric Disease*

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ABSTRACT Objective: To explore the differential expression and diagnostic value of serum globulin/cholinesterase (G/C) and vascular endothelial cell growth factor (VEGF) in patients with different severity levels of cirrhosis and portal hypertensive gastric disease. **Methods:** 80 patients with cirrhotic portal hypertension and gastric disease admitted to our hospital from December 2020 to December 2023 were selected as the study subjects. They were divided into mild group (n=45) and severe group (n=35) according to the severity of the disease. Additionally, 40 patients with cirrhotic portal hypertension and no accompanying gastric disease admitted during the same period were selected as the control group. Compare the clinical data and G/C, VEGF expression levels of three groups of patients, use logistic regression model to analyze the independent influencing factors of cirrhotic portal hypertension gastric disease, and use Pearson test to analyze the correlation between G/C, VEGF and different severity of cirrhotic portal hypertension gastric disease. Finally, establish ROC curve to analyze the diagnostic value of G/C, VEGF for cirrhotic portal hypertension gastric disease. **Results:** There were no differences in gender, age, comorbidities, etiology, Child Pugh grading, AST, and ALT levels among the three groups of patients ($P>0.05$), while there were differences in the course of liver cirrhosis, Hb, PLT, Alb, G/C, and VEGF levels ($P<0.05$); Elevated G/C and decreased VEGF were independent influencing factors for portal hypertensive gastric disease in liver cirrhosis($P<0.05$); The expression of G/C (r=0.493) and VEGF (r=-0.542) is closely related to the severity of portal hypertensive gastric disease in patients with cirrhosis ($P<0.05$); The area under the diagnostic curve of VEGF for portal hypertensive gastropathy in liver cirrhosis is 0.822, and the optimal diagnostic threshold is 143.45 ng/mL. The area under the diagnostic curve of G/C for portal hypertensive gastropathy with cirrhosis is 0.875, and the opti-

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mal diagnostic threshold is 0.87. The area under the curve of the combination of the two is 0.932. The diagnostic sensitivity and specificity of G/C combined with VEGF for portal hypertensive gastric disease in cirrhosis were significantly higher than those of a single indicator (P<0.05). **Conclusion:** G/C and VEGF are independent influencing factors of portal hypertension in patients with liver cirrhosis, and are significantly correlated with different severity levels. The combination of the two can improve the diagnostic efficacy of portal hypertension in patients with liver cirrhosis.

Key words: Serum globulin/cholinesterase; Vascular endothelial cell growth factor; Cirrhotic portal hypertensive gastropathy; Liver cirrhosis; Diagnostic value

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前言

肝硬化发生早期患者多肝脏代偿功能较强，并无显著临床症状，后期随着门脉高压和肝功能持续损害的发生，并发症发生率持续增加[1]。其中肝硬化门脉高压胃病作为常见并发症之一，患者多出现胃黏膜糜烂、水肿、淤血等情况，胃镜诊断可发现胃黏膜呈马赛克样改变，患者出现消化道出血、腹痛、腹胀、食欲不振等症状，严重影响患者日常生活[2,3]。当前针对肝硬化门脉高压胃病多采取胃镜诊断为主，但胃镜作为创伤性诊断方式，不适宜反复进行。因此，越来越多学者推荐对肝硬化门脉高压胃病采取相关血液指标进行评价[4]。血清胆碱及血清球蛋白的检测结构不易受到治疗及外界因素影响，可通过血清球蛋白/胆碱酯酶(G/C)反映肝功能状态，从而评价肝硬化疾病的发展情况[5]。另外，血管内皮细胞生长因子(VEGF)能够通过促进血管增生，在血管形成过程中具有重要作用，研究显示[6,7]，门脉高压性胃病患者胃黏膜 VEGF 水平会出现显著变化，但 G/C、VEGF 两者是否可评价肝硬化门脉高压胃病严重程度，并对其进行诊断尚无确切定论。因此，本研究探讨 G/C、VEGF 在不同病情严重程度肝硬化门脉高压性胃病患者中的表达差异及其疾病诊断价值，具体报道如下。

1 资料与方法

1.1 一般资料

选取我院 2020 年 12 月到 2023 年 12 月收治的 80 例肝硬化门脉高压性胃病患者作为研究对象，依照患者肝硬化门脉高压性胃病严重程度进行分组，分为轻度组（n=45）及重度组（n=35），另选取同期收治的肝硬化门脉高压未合并胃病的 40 例患者作为对照组。本研究经我院伦理委员会批准。

1.2 纳排标准

纳入标准：符合肝硬化诊断标准[8]，且经过腹部磁共振、电子胃镜等临床综合诊断确诊为肝硬化门静脉高压胃病[9]；临床资料完整；年龄≥18 岁；对本研究知情同意。

排除标准：合并恶性肿瘤、肾衰竭、呼吸衰竭、心力衰竭等严重基础疾病者；合并免疫功能类疾病者；合并血液疾病者；有脾动脉介入栓塞术史者；近 3 个月内出现消化道出血者；合并肝肾综合征、肝性脑病等严重并发症者。

1.3 方法

肝硬化门脉高压性胃病严重程度判定方法：对所有患者采用 Olympus-CV-290 胃镜进行检查，黏膜呈现猩红热疹、糜烂、充血水肿等症状，同时伴随弥漫性出血胃炎，肿胀胃黏膜上出现樱桃红样斑点，并出现白色网络格样改变，与蛇皮样花纹类似可确诊为肝硬化门脉高压性胃病。并针对患者胃镜检查结果及改良分级系统对其严重程度进行分级。其中出现樱桃红色斑点、红色病变或黑褐色斑点黏膜图案为重度；无樱桃红色斑点、红色病变或黑褐色斑点黏膜图案为轻度。

G/C、VEGF 检测方法：抽取所有患者空腹静脉血 3 mL，离心后取上清液，应用日本 HTACHI 7600 Series 全自动生化分析仪检测血清胆碱酯酶及血清球蛋白表达水平，并计算血清球蛋白/胆碱酯酶(G/C)比值。应用化学发光法检测血管内皮细胞生长因子(VEGF)表达水平，检测步骤严格依照试剂盒(生产企业：威高生物)说明书进行。

一般资料收集：收集所有患者一般临床资料及相关血液指标表达水平，其中包括：性别、年龄、合并基础疾病、病因、Child-Pugh 分级、谷草转氨酶(AST)、谷丙转氨酶(ALT)、血红蛋白(Hb)、血小板(PLT)、白蛋白(Alb)。

1.4 统计学方法

应用 SPSS20.0 软件分析数据，以 $\bar{x}\pm s$ 表示计量资料，t 检验；计数资料用百分比表示，采用 x^2 检验，P<0.05 为差异具有统计学意义。采用 Pearson 检验进行相关性分析；采用 logistics 回归模型分析肝硬化门脉高压性胃病的独立影响因素。

2 结果

2.1 一般资料与 G/C、VEGF 表达水平对比

三组患者性别、年龄、合并基础疾病、病因、Child-Pugh 分级、AST、ALT 水平对比无明显差异(P>0.05)，肝硬化病程、Hb、PLT、Alb、G/C、VEGF 水平对比差异显著(P<0.05)，见表 1。

2.2 肝硬化门脉高压性胃病的独立影响因素分析

以单因素分析具统计学意义因素纳入多因素分析，结果显示，G/C 升高、VEGF 降低为肝硬化门脉高压性胃病的独立影响因素(P<0.05)，见表 2。

2.3 G/C、VEGF 与不同病情严重程度肝硬化门脉高压性胃病的相关性

G/C(r=0.493)、VEGF(r=-0.542)的表达均与肝硬化门脉高压性胃病严重程度密切相关(P<0.05)，见表 3。

2.4 G/C、VEGF 对肝硬化门脉高压性胃病的诊断价值

VEGF 对肝硬化门脉高压性胃病的诊断曲线下面积为 0.822，最佳诊断界限值为 143.45 ng/mL。G/C 对肝硬化门脉高压性胃病的诊断曲线下面积为 0.875，最佳诊断界限值为 0.87。两者联合的曲线下面积为 0.932。G/C 联合 VEGF 对肝硬化门脉高压性胃病的诊断灵敏度与特异度明显高于单一指标(P<0.05)，见图 1、表 4。

表 1 三组患者一般资料与 G/C、VEGF 表达水平对比

Table 1 Comparison of General Information and G/C, VEGF Expression Level

Index	Mild group(n=45)	Severe group(n=35)	Control group(n=40)	x^2/F	*P*
Gender (n)					
Male	27	21	25	0.050	0.817
Female	18	14	15		
Age (years)	51.30± 4.57	52.29± 5.42	52.17± 5.86	1.261	0.221
Course of liver cirrhosis (years)	4.25± 1.23	5.36± 1.57	3.25± 0.68	7.356	<0.001
Underlying disease					
Hypertension	12	7	11	1.160	0.282
Diabetes	8	10	9	0.050	0.815
Etiology					
Other	8	5	7	0.690	0.493
Virus hepatitis	37	30	33		
Child-Pugh grade					
A	26	20	22	0.202	0.840
B	16	13	17		
C	3	2	1		
Hb(g/L)	112.39± 12.28	125.81± 13.04	132.45± 15.75	16.756	<0.001
AST(U/L)	45.02± 6.79	44.47± 8.84	44.77± 9.47	0.437	0.508
ALT(U/L)	36.82± 5.73	35.30± 7.09	35.77± 8.47	0.469	0.640
PLT(× 10^9/L)	88.85± 12.68	57.35± 11.63	51.53± 10.47	21.714	<0.001
Alb(g/L)	35.31± 6.75	39.46± 7.48	32.75± 6.88	8.884	<0.001
G/C	1.04± 0.13	1.37± 0.28	0.68± 0.11	28.964	<0.001
VEGF(ng/mL)	168.46± 31.68	145.78± 23.67	137.35± 24.74	32.049	<0.001

表 2 肝硬化门脉高压性胃病的独立影响因素分析

Table 2 Analysis of independent influencing factors of portal hypertensive gastric disease in patients with liver cirrhosis

Index	β	SE(β)	Wald x^2	OR	95%CI	*P*
The course of liver cirrhosis	1.354	0.387	1.145	1.241	0.784~1.756	0.551
Hb	1.457	0.384	1.265	2.791	1.457~5.745	0.345
PLT	1.246	0.231	1.757	2.146	1.534~3.693	0.241
Alb	1.231	0.412	1.787	0.857	0.542~1.536	0.425
G/C	2.313	0.652	3.135	1.789	1.447~3.682	<0.001
VEGF	3.241	0.642	4.636	2.845	1.726~4.361	<0.001

表 3 G/C、VEGF 与不同病情严重程度肝硬化门脉高压性胃病的相关性

Table 3 Correlation between G/C, VEGF and portal hypertensive gastric disease with different severity of liver cirrhosis

Index	Severity of portal hypertensive gastric disease in patients with liver cirrhosis	
	r	*P*
G/C	0.493	<0.01
VEGF	-0.542	<0.01

表 4 G/C、VEGF 对肝硬化门脉高压性胃病的诊断价值

Table 4 Diagnostic value of G/C and VEGF for portal hypertensive gastric disease in liver cirrhosis

Index	AUC	95%CI	Error	*P*	Optimal threshold	Sensitivity(%)	Specificity(%)	Youden index
VEGF	0.822	0.504~0.823	0.018	0.025	143.45 ng/mL	61.00	53.00	0.642
G/C	0.875	0.472~0.857	0.089	0.037	0.87	75.00	67.00	0.731
The combination of the two	0.932	0.678~1.243	0.024	0.012	-	83.00	92.00	0.871

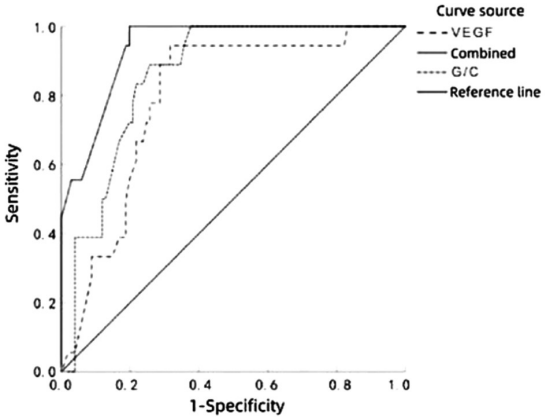

图 1 G/C、VEGF 对肝硬化门脉高压性胃病的诊断 ROC 曲线

Fig.1 ROC curve of G/C and VEGF in the diagnosis of portal hypertensive gastric disease in liver cirrhosis

3 讨论

据统计[10],我国为病毒性肝炎高发国家之一,除了乙型肝炎之外,丙型肝炎也会随着病情的发展逐渐成为肝硬化。肝脏纤维化致病因子会造成肝内结缔组织异常增生，形成纤维隔,导致肝脏变性或失去活性,形成肝硬化[11,12]。对于肝硬化门脉高压患者症状多以食欲减退、上腹部隐痛为主,其中门静脉压力增高也是肝硬化门脉高压性胃病发生的主要原因[13,14]。肝硬化为各种慢性肝病晚期阶段,门静脉高压和肝功能受损为主要特征。另外研究发现[15],肝硬化门脉高压性胃病还会随着胃肠道黏膜和血流动力学变化引起慢性或急性消化道出血,其中慢性出血发生率约为 3%~26%,急性出血发生率约为 2%~12%。早期内镜下诊断肝硬化门脉高压性胃病的严重程度可有助于评估患者出血风险,然而消化道内镜不能常规评价未明确是否存在肝硬化门脉高压性胃病的患者,所以,急需一种非侵入性方法来诊断、评价肝硬化门脉高压性胃病的发生概率与严重性,进而评价患者出血风险[16-18]。因此,本研究针对我院肝硬化门脉高压性胃病患者采取 G/C、VEGF 两种指标进行诊断与评估,以期为临床提供参考意见。

本研究结果表明，肝硬化病程、Hb、PLT、Alb、G/C、VEGF 水平对比差异显著($P<0.05$)。Hb 作为红细胞中的蛋白质,为血常规重要检测指标，不仅可反应人体生成红细胞的能力,其水平降低可能由于肝硬化或肝炎导致。另外,Gavriilidis P 等[19]研究显示,随着肝硬化的发生与发展,Alb 合成功能受限,随着肝硬化疾病严重程度加重，腹胀、食管静脉曲张等症状发生,Alb 水平会出现持续下降趋势,与本研究结果相符。本研究结果显示,不同严重程度肝硬化门脉高压患者 G/C 水平出现明显差异,与 Giri S 等[20]研究结果部分一致。Giri S 等研究结果显示,肝硬化患者 G/C 水平会明显高于健康人群,但其与肝硬化门脉高压性胃病的关系尚无确切定论。笔者认为,肝硬化门脉高压性胃病患者 G/C 水平升高可能是因为,G/C 比值可真实的反映肝脏炎性反应程度与免疫功能，且不受外界环境影响,精准评价肝脏合成储备能力,反应肝功能状态,因此也可在评价肝硬化严重程度的同时,进一步评价患者胃病严重程度[21]。另外,本研究发现不同肝硬化门脉高压胃病患者 Child-Pugh 分级并无显著差异,这可能是因为门静脉高压虽然为肝硬化门脉高压胃病的发病机制,但与肝硬化严重程度并无显著关系。也可能是因为,本研究数据样本量过少带来的研究局限,还需日后增加样本量持续深入分析。另外,研究发现[22],微血管形态结构异常为肝硬化门脉高压胃病的病理学基础,血管内皮增厚会扩大损伤因子作用靶点，导致胃黏膜对于损伤因子易感性增强,而动静脉短路导致胃黏膜血液灌注不良,增加胃黏膜出血发生率，因此肝硬化门脉高压胃病患者会出现 VEGF 水平升高现象，与本研究结果相符。本研究进一步分析表明,G/C 升高、VEGF 降低为肝硬化门脉高压性胃病的独立影响因素($P<0.05$),与 Cai C 等[23]研究结果具有一定相似性。因此也提示临床上针对 G/C 升高和 / 或 VEGF 降低的肝硬化患者要警惕肝硬化门脉高压性胃病的发生,及时采取相关措施进一步预防患者胃黏膜出血情况。本研究显示,G/C(r=0.493)、VEGF(r=-0.542)的表达均与肝硬化门脉高压性胃病严重程度密切相关($P<0.05$)。分析原因为,VEGF 作为最强烈致血管通透性增加因子,能够导致微血管通透性增加,促使血浆外渗,导致胃黏膜上皮细胞间隙红细胞数目增加,从而间接判定患者疾病严重程度[24]。另外目前虽然部分研究证实 G/C 水平与肝硬化严重程度相关,但其针对,肝硬化门脉高压性胃病严重程度的判断尚无确切定论[25]。而本研究发现,G/C 与肝硬化门脉高压性胃病严重程度相关可能与患者病情加重,门静脉高压增加具有一定关系,但具体机制还需日后持续加深研究。最后本研究结果表明,G/C 联合 VEGF 对肝硬化门脉高压性胃病的诊断灵敏度与特异度明显高于单一指标($P<0.05$),证明临床可考虑应用 G/C 联合 VEGF 来为肝硬化门脉高压性胃病进行辅助诊断。

综上所述,G/C、VEGF 为肝硬化门脉高压性胃病的独立影响因素,且与不同病情严重程度具有显著关系,两者联合可提升度肝硬化门脉高压性胃病的诊断效能。

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