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血清间皮素联合 CDK6 诊断早期卵巢癌的临床价值研究 *

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摘要 目的:探讨血清间皮素联合 CDK6 诊断早期卵巢癌的临床价值。**方法:**选择 2014 年 6 月～2017 年 6 月就诊于我院妇产科的 51 例 Ⅰ～Ⅱ期卵巢癌患者 (实验组) 及同期经病理确诊为正常卵巢组织的 43 例患者 (对照组) 为研究对象，检测和比较其血清 MSLN、CA125、CA199、HE4、VEGF-C 水平及卵巢癌组织 CDK6 的表达。采用多因素 logistic 回归进一步分析两种间上述有显著差异的指标。同时，对新指标与血清 CA125、CA199 水平进行相关性分析，ROC 曲线分析其对早期卵巢癌的诊断价值。**结果:**实验组血清 MSLN、CA125、CA199、HE4、VEGF-C 水平及 CDK6 表达均显著高于对照组(P＜0.05)。多因素 logistic 分析结果显示血清 MSLN、CA125、CDK6 表达对早期卵巢癌的诊断有价值(P<0.05)，且血清 CA125 的影响程度最高(RR=1.421)。卵巢癌患者血清 MSLN(r=0.573，P=0.013)和卵巢癌组织 CDK6 表达(r=0.412，P=0.037)与 CA125 呈正相关关系。ROC 曲线提示血清 MSLN、CDK6 表达、血清 CA125 及 MSLN 联合 CDK6 诊断早期卵巢癌的 ROC 曲线下面积分别为 0.639、0.700、0.715、0.765，MSLN 联合 CDK6 的曲线下面积最大。**结论:** 血清 MSLN 联合癌组织 CDK6 的表达诊断早期卵巢癌的临床价值明显优于常规血清学指标 CA125、CA199。

关键词:血清间皮素;CDK6;CA125;早期卵巢癌诊断

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Clinical Value of Serum Albumin Combined with CDK6 in the Diagnosis of Early Ovarian Cancer*

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ABSTRACT Objective: To explore the clinical value of serum mesothelin conbined with CDK6 in the diagnosis of early ovarian cancer. **Methods:** 51 cases of patients who were diagnosed as stage Ⅰ～Ⅱ ovarian cancer (experimental group) in the department of obstetrics and gynecology of our hospital from June 2014 to June 2017 and 43 cases of patients with normal ovarian tissue were diagnosed by pathology(control group) and selected as the research object. The serum MSLN, CA125, CA199, HE4, VEGF-C levels and CDK6 expression of ovarian tissue were detected and compared. The significantly different indicators between the two groups were further analyzed by multifactor logistic regression. At the same time, the correlative analysis between the new index and the serum CA125, CA199 levels were carried out, the diagnostic value for early ovarian cancer was analyzed by ROC curve. **Results:** The serum MSLN, CA125, CA199, HE4, VEGF-C levels and CDK6 expression of experimental group were significantly higher in the experimental group than those of the control group (P<0.05). Multifactor logistic regression showed that serum MSLN, CA125 levels and CDK6 expression were valuable in the diagnosis of early ovarian cancer (P<0.05), and the serum CA125 had the highest impact(RR=1.421). The serum MSLN level of ovarian cancer patients(r=0.573, P=0.013) and the CDK6 expression of the Ovarian tissue (r=0.412，P=0.037) were positively correlated with serum CA125 level. ROC curves indicated that the area of the ROC curve of serum MSLN, CDK6 expression, serum CA125 and MSLN combined with CDK6 were 0.639, 0.700, 0.715 and 0.765, The area under the curve of MSLN combined with CDK6 was the highest. **Conclusion:** The clinical value of serum MSLN combined with CDK6 expression in the ovarian cancer tissue for the diagnosis of early ovarian cancer was superior to the conventional serological index CA125, CA199.

Key words: Serum mesothelin; CDK6; CA125; Early ovarian cancer; Diagnosis

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卵巢癌是妇科恶性肿瘤中较为常见的一种，发病率仅次于宫颈癌和子宫内膜癌，死亡率居各类女性生殖系统恶性肿瘤之首，严重威胁女性健康和生命[1,2]。卵巢癌起病隐匿，早期症状不典型，诊断困难[3,4]，70%的初诊患者确诊时已属中晚期，75%的初治患者经规范化治疗后可获得完全缓解[5,6]，但 70%获得临床完全缓解的患者仍会复发，其 5 年生存率仅约 30%[7]。而早期诊

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断的卵巢癌患者,其 5 年生存率可达 90%[8],可见提高卵巢癌的早期诊断率对于治疗处理及预后至关重要。

目前,临床上诊断早期卵巢癌主要通过影像学检查、盆腔检查以及人附睾蛋白 4(HE4)、糖类抗原 CA125 等血清学标志物检测[9-11]。然而这些检查手段用于卵巢癌早期诊断的特异性和敏感性不够理想[12,13]。因此,寻找一种敏感性和特异性较强的卵巢癌诊断指标一直是当前妇产科研究的热点。Badgwel 等[14]研究表明血清间皮素(Mesothelin,MSLN)与卵巢癌的发生、转移密切相关。凌晨[15]等研究表明 CDK6 过表达与早期卵巢癌发生发展密切相关。但两者诊断效能尚未被充分认识,且两者联合用于诊断早期卵巢癌的相关研究较少。因此,本研究以卵巢癌患者为研究对象,主要探讨了血清 MSLN 联合 CDK6 对卵巢癌早期诊断的临床价值,旨在为临床应用血清 MSLN 联合 CDK6 诊断早期卵巢癌提供依据。

1 对象与方法

1.1 研究对象

选取 2014 年 6 月～2017 年 6 月在我院妇产科住院治疗的经术后病理确诊为Ⅰ~Ⅱ期卵巢癌的患者 51 例 (实验组)为研究对象,患者年龄 32~65 岁,平均(47.12± 13.33)岁。选取同期经病理确诊为正常卵巢组织的患者 43 例作为对照组,患者年龄 29~61 岁,平均(44.32± 11.67)岁。研究对象本人或家属签署知情同意书,本实验符合医院伦理委员会要求并通过审批。纳入标准:⑴ 经病理检查确诊;⑵ 肝、肾功能正常。排除标准:⑴ 具有其他肿瘤病史;⑵ 临床资料及病理标本不齐全。

1.2 研究方法

1.2.1 CDK6 的表达检测 收集所有患者卵巢石蜡组织标本,CDK6 的表达检测采用免疫组化检测:⑴ 取所有患者石蜡切片置于烤箱中烘烤后将切片浸入二甲苯中脱蜡,再将切片浸入酒精中水化,然后置于超纯水中待用;⑵ 将切片放入盛有柠檬酸盐抗原修复液的孵育槽中,然后将孵育槽放入高压锅中高温高压修复,室温自然冷却;⑶ 依次滴加卵白素、d- 生物素溶液、内源性过氧化物酶阻断剂、山羊血清、CDK6 抗体、羊抗兔 IgG 和链霉素抗生物素蛋白 - 过氧化物酶溶液于切片中,每次滴加一种试剂后室温孵育 10 min,每次滴加下一种试剂前磷酸盐缓冲液洗 3 次;⑷ 滴加 DAB 液,然后将切片于显微镜下观察,显色约 20 s 后再将切片置于水中中止显色;⑸ 将切片置于苏木素中复染、流水中冲洗返蓝后浸入酒精中脱水;⑹ 中性树胶封片,显微镜下观察染色效果。免疫组化评分分别对胞浆和胞核单独进行,蛋白表达量综合计分为两者评分之和,总分为 12 分。

1.2.2 血清学指标 留取受试者入院后空腹静脉血 3~5 mL,3000 r / min 离心 10 min 分离血清。血清 MSLN 和 VEGF-C 水平测定采用酶联免疫吸附试验,前者参考范围为 0.0~4.6 ng/ml,后者参考范围为 67.4~270.0 pg/mL。血清 CA125 和CA199 水平测定采用化学发光免疫分析仪,前者参考范围为 0.0~35.0 u/ml,后者参考范围为 0.0~37.0 μ/mL。血清 HE4 水平测定采用电化学发光免疫分析仪,其考范围为 0.0~150.0 pmol/L。

1.3 临床资料收集

收集两组患者年龄、体重指数(BMI)、身高、经产、绝经、月经期≤ 4 d 等一般资料;血清 MSLN、CA125、CA199、HE4、血管内皮生长因子 C(VEGF-C)水平等血清学指标及 CDK6 表达免疫组化评分结果等诊断指标。

1.4 统计学分析

采用 SPSS 19.0 统计软件进行分析。计量资料用 MEAN± SD 表示,两组间比较采用独立样本 t 检验。计数资料间比较采用 x^2 检验,将初步筛选出的有明显差异的指标进行多因素 Logistic 回归分析,以研究其对早期卵巢癌诊断的价值程度。对有价值的新指标和传统指标进行相关性分析,分析新指标和传统指标的关系。建立 ROC 曲线,再次通过 logistic 回归模型,形成新的联合诊断因子,分析上述联合指标对早期卵巢癌的诊断价值。所有结果以 $p<0.05$ 表示为差异有统计学意义。

2 结果

2.1 两组患者一般临床资料的比较

本研究共纳入 94 例患者,其中实验组 51 例,对照组 43 例。与对照组相比,实验组 BMI 显著升高,经产、绝经患者比例降低、月经期≤ 4 d 患者比例增加,差异均有统计学意义(P＜0.05)。两组患者年龄、身高相比差异均无统计学意义(P>0.05),详见表 1。

表 1 两组患者的一般临床资料比较

Table 1 Comparison of the clinical and general data between two groups

	Experimental group (n=51)	Control group (n=43)	P
Age (year)	47.12± 13.33	44.32± 11.67	0.286
BMI(kg/m^2)	24.21± 2.81	22.14± 2.14	0.000
Height(cm)	159.51± 9.82	156.51± 8.63	0.095
Reproductive history	35	37	0.047
Menopause	11	18	0.034
Menstrual period is less than 4 d	16	6	0.047

2.2 两组患者血清学指标及 CDK6 表达评分的比较

实验组血清 MSLN、CA125、CA199、HE4、VEGF-C 水平及 CDK6 表达均显著高于对照组(P＜0.05),见表 2。

2.3 多因素 logistic 回归分析

进一步分析患者血清 MSLN、CA125、CA199、HE4、VEGF-C 水平及 CDK6 表达对早期卵巢癌诊断的价值,多因素

logistic 分析结果显示：血清 MSLN、CA125、CDK6 对早期卵巢癌的诊断有价值(P<0.05)；HE4、CA199 及 VEGF-C 对早期卵巢癌的诊断价值不大(P>0.05)。分析各诊断指标对早期卵巢癌诊断的价值程度，CA125 的价值程度最高 (RR=1.421)，其次为 MSLN(RR=1.372)，而 CDK6 表达(RR=1.294)的价值程度则稍逊一筹。详见表 3。

表 2 两组患者血清学指标及 CDK6 表达评分的比较

Table 2 Comparison of the serological indicators and CDK6 expression scores between two groups

	Experimental group (n=51)	Control group (n=43)	P
MSLN(ng/mL)	6.28± 1.02	3.54± 0.54	0.000
CA125(μ/mL)	212.74± 27.71	50.64± 6.72	0.000
CA199(μ/mL)	190.64± 21.79	22.63± 3.74	0.000
HE4(pmol/L)	410.63± 58.63	159.74± 15.84	0.000
CDK6 expression scores	4.88± 1.12	3.69± 0.72	0.000
VEGF-C(pg/mL)	1580.74± 129.64	310.63± 25.74	0.000

表 3 诊断指标的 logistic 分析

Table 3 Logistic model analysis of the diagnostic indicators

	B	SE	Wald	df	P	OR	95.0% CI	
							Lower limit	Upper limit
MSLN	0.316	0.074	5.478	1	0.024	1.372	1.187	1.586
CA125	0.351	0.021	6.493	1	0.013	1.421	1.364	1.481
CA199	0.176	0.413	3.871	1	0.297	1.193	0.531	2.680
HE4	0.216	0.284	4.264	1	0.062	1.241	0.711	2.165
CDK6	0.258	0.123	4.735	1	0.036	1.294	1.017	1.647
VEGF-C	0.196	0.381	4.104	1	0.186	1.217	0.577	2.568

2.4 受试者血清 MSLN 水平和 CDK6 表达评分与血清 CA125 水平的相关性分析

采用 Pearson 相关性分析分析血清 MSLN 水平、CDK6 表达评分与血清 CA125 水平的相关性，由表 4 可知，MSLN 与 CA125 呈正相关关系(r=0.573，P=0.013)；CDK6 与 CA125 亦呈正相关关系(r=0.412，P=0.037)。

表 4 新旧诊断指标间的相关性分析

Table 4 Analysis of the correlation between old and new diagnostic indicators

	CA125	
	r	P
MSLN	0.573	0.013
CDK6	0.412	0.037

2.5 血清 MSLN、CDK6 表达、MSLN 联合 CDK6 及血清 CA125 诊断早期卵巢癌的 ROC 曲线分析

ROC 结果提示：血清 MSLN、CDK6 表达、血清 CA125 及 MSLN 联合 CDK6 诊断早期卵巢癌的 ROC 曲线下面积分别为 0.639、0.700、0.715、0.765，MSLN 联合 CDK6 的 AUC 最高，见图 1。

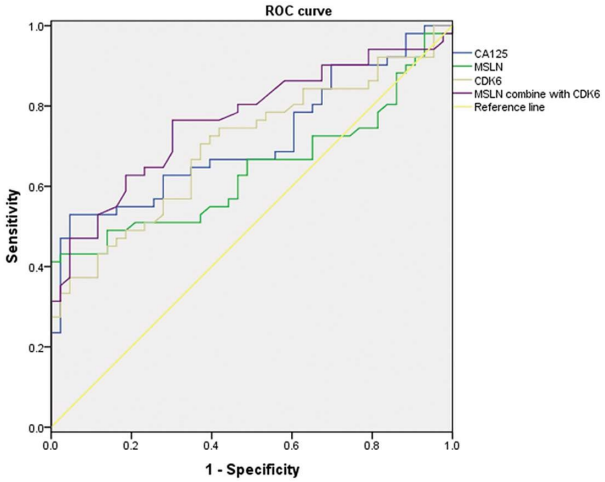

图 1 MSLN、CDK6、MSLN 联合 CDK 及 CA125 诊断早期卵巢癌的 ROC 曲线分析

Fig. 1 The ROC curves of MSLN, CDK6, MSLN combines with CDK6 and CA125 in diagnosis of patients with early ovarian cancer

3 讨论

卵巢癌是常见的妇科恶性肿瘤，具有发病率高、早期诊断困难、五年生存率低、易转移易复发、死亡率高等特点，早期诊断并积极治疗能明显改善患者预后[16-19]。目前，临床上诊断卵巢癌最常用的血清学指标为 CA125，但其敏感性低，尤其对于早期卵巢癌患者[20]。卵巢癌患者至少有 20%血清 CA125 水平正

常,而Ⅰ期卵巢癌患者有50%血清CA125水平正常。此外其特异性也不够高[21],一些妇科非恶性肿瘤患者如盆腔炎症性疾病、子宫内膜异位症、早期妊娠等,还有一些非妇科疾病患者如肝硬化、胰腺癌、先天性心脏病等患者血清CA125水平也会升高[22]。近年来,HE4是美国食品药品管理局唯一新批准的用于诊断卵巢癌的标志物,其诊断卵巢癌特异度较CA125高,但是其敏感度较CA125低[23],且其血清水平与年龄、吸烟、肾功能及绝经有关,故不足以成为诊断卵巢癌的独立标志物,常作为CA125的补充[24]。寻找敏感性和特异性较强的肿瘤标志物仍然是现阶段卵巢癌临床研究的重点之一。既往研究表明卵巢癌的发病危险因素主要包括家族遗传史、生育因素、月经史、哺乳、运动、饮食、妇科疾病及心理因素等[25,26]。本研究中,卵巢癌患者BMI显著升高,经产、绝经患者比例降低、月经期≤4 d患者比例增加,与上述观点基本相符。

CDK6是一个关键性的细胞周期促进因子,编码38kD的蛋白质,诱导细胞周期由G1向S期转化,参与诱导肿瘤细胞的增殖[27,28]。凌晨等研究表明CDK6促进了早期卵巢癌发生发展。MSLN是一种细胞表面糖蛋白,正常情况下仅在胸膜间皮、心包和腹膜等间皮细胞上表达,而在一些恶性肿瘤中也见有高表达,如恶性间皮瘤和胰腺癌等。Hassan[29]等研究发现70%的卵巢癌患者MSLN高水平表达,表明其可能具有诊断卵巢癌的作用。CA199是一种低聚糖类抗原,能被抗人结肠癌细胞株抗体所识别,对胰腺癌和肝胆管癌等消化道肿瘤敏感性较高,诊断价值明确。近年来有研究显示多数卵巢癌患者血清CA199水平升高,提示其也可以作为诊断卵巢癌的肿瘤标志物,并有相关研究表明CA199虽然在诊断浆液性卵巢癌时敏感性低,但其对黏液性卵巢癌敏感性高,可达78%[30]。VEGF-C是从人前列腺癌细胞株中分离出来的特异性淋巴管内皮生长刺激因子,为VEGF的一种新同源物,有研究表明VEGF-C可促进卵巢癌细胞转移,提示其参与诱导卵巢癌淋巴结转移[31]。

本研究选取CDK6、MSLN、CA199和VEGF-C等可能作为诊断早期卵巢癌的新标志物以及CA125和HE4等目前临床上用于诊断卵巢癌的传统标志物进行研究,分别对其进行单因素分析,初步筛选出可能存在显著影响的指标。结果显示:卵巢癌患者上述指标均明显高于对照人群,提示上述所有指标均有作为诊断卵巢癌标志物的希望。将初步筛选出的有明显差异的指标进行多因素Logistic回归分析,以研究其对早期卵巢癌诊断的价值程度。分析结果显示:血清MSLN、CA125、CDK6对早期卵巢癌的诊断有价值,提示上述指标可作为早期卵巢癌的诊断指标,对比三者对诊断的价值程度,CA125的价值程度最高,其次为MSLN,CDK6表达稍逊一筹;HE4、CA199及VEGF-C对早期卵巢癌的诊断价值不大。

将新指标与传统指标进行相关性分析,不仅可以得出新指标与传统指标是否存在一定的关联,还可以在一定程度上提示新指标是否也能用于诊断。CA125为目前临床上诊断卵巢癌最常用的传统指标,故在本研究将筛选出来的新指标MSLN、CDK6与传统指标CA125做相关性分析,结果显示MSLN和CDK6均与CA125呈正相关关系,提示MSLN和CDK6也可用于早期卵巢癌的诊断。绘制血清MSLN、CDK6表达、MSLN联合CDK6及血清CA125诊断早期卵巢癌的ROC曲线,结果显示MSLN联合CDK6的曲线下面积最高。这提示上述指标对早期卵巢癌均具有一定的诊断价值,MSLN联合CDK6诊断效能最高,比传统指标CA125诊断效能高,可考虑作为早期卵巢癌诊断的辅助指标。

不同的研究选取不同的指标,不同的研究得出的诊断早期卵巢癌指标的诊断效能也存在差异,这不仅反映了早期卵巢癌诊断困难,也反映了各研究病例选择的差异。本研究尚存在不足,研究对象人数较少,纳入可能诊断早期卵巢癌的指标较少,并未将新指标与传统指标进行联合。在后续研究中,我们将进一步增加样本数量,尽可能纳入更多诊断指标,将新指标与传统指标进行联合诊断,进一步提高卵巢癌的早期诊断率。

综上所述,本研究结果表明血清MSLN水平联合卵巢组织CDK6的表达诊断早期卵巢癌价值明显优于常规血清学指标。

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