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❖临床研究❖

血清人附睾蛋白和癌抗原 125 联合预测上皮性卵巢癌术后复发的价值分析

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【摘要】**目的**:分析上皮性卵巢癌患者减灭手术前后血清人附睾蛋白(HE4)和癌抗原 125(CA125)水平及 CA125/HE4 比值变化,初步探索其对于预测疾病复发的价值。**方法**:按复发与否将 50 例行肿瘤细胞减灭术并接受术后规范性化疗的上皮性卵巢癌(EOC)患者分为复发组($n=22$)和非复发组($n=28$)。比较两组在术前、术后 1、3、及 6 个月各时间点 HE4、CA125 水平、CA125/HE4 比值变化及其与 EOC 复发的关系。**结果**:两组国际妇产科联盟(FIGO)分期比较,差异具有统计学意义($P<0.05$)。两组 HE4、CA125 水平在术后各时间点均呈逐渐下降趋势($P<0.05$)。术前,复发组 HE4、CA125 水平均高于非复发组($P<0.05$)。术后 3 个月,复发组 HE4 水平低于非复发组($P<0.05$),CA125/HE4 比值高于非复发组,差异有统计学意义($P<0.05$)。单因素 Logistic 回归分析显示,FIGO 分期、术前高水平的 HE4、CA125 可能是 EOC 复发的危险因素($P<0.05$)。受试者工作特征曲线(ROC)显示,术前 HE4、CA125 预测疾病复发的 ROC 曲线下面积(*AUC*)分别为 0.964(95% *CI*:0.908~1.000)、0.849(95% *CI*:0.742~0.956),差异无统计学意义($P>0.05$);术前 HE4、CA125 及二者联合预测复发的敏感度(86.4% *vs*. 72.7% *vs*. 90.9%),特异度(100% *vs*. 85.7% *vs*. 100%)。**结论**:血清 HE4 联合 CA125 对于检测 EOC 复发具有一定的价值,术前 HE4、CA125 较高的患者可能面临更高的卵巢癌复发风险。

【关键词】卵巢癌;人附睾蛋白;癌抗原 125;复发;上皮性卵巢癌;预测;诊断
【中图分类号】R737.31;R730.43 【文献标志码】A

Value analysis of HE4 and CA125 combined to predict the recurrence of epithelial ovarian cancer

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【**Abstract**】**Objective**: To analyze the changes of serum HE4 and CA125 and the ratio of CA125/ HE4 in patients with epithelial ovarian cancer (EOC) before and after subtractive surgery, and explore their value for predicting disease recurrence. **Methods**: A total of 50 patients with EOC who undergoing cytoreductive surgery and standard postoperative chemotherapy were selected, and they were divided into the recurrence group ($n=22$) and the non-relapse group ($n=28$) according to recurrence or not. The changes of serum HE4 and CA125 levels, and the ratio of CA125/ HE4 and relationship between the recurrence of EOC were compared between the two groups before operation, 1, 3 and 6 m after operation. **Results**: Compared in International Federation of Obstetrics and Gynecology (FIGO) staging of the two groups, the difference was statistically significant ($P<0.05$). The levels of HE4 and CA125 in the recurrence group and the non- relapse group showed a gradual downward trend at the postoperative time point ($P<0.05$). Before surgery, levels of HE4 and CA125 in the recurrence group were higher than those in the non- relapse group ($P<0.05$). 3 months after operation, the levels of HE4 in the recurrence group was lower than that in the non-relapse group ($P<0.05$), the ratio of CA125/HE4 in the recurrence group was higher than that in the non-relapse group, the difference were statistically significant ($P<0.05$). Univariate Logistic regression analysis showed that FIGO stage, preoperative serum HE4, CA125 may be the risk factor for recurrence of EOC ($P<0.05$). The ROC curve showed that the *AUC*s of preoperative HE4 and CA125 in predicting disease recurrence were 0.964 (95% *CI*:0.908~1.000) and 0.849 (95% *CI*:0.742~0.956), and there was no significant difference between them ($P>0.05$). The sensitivity of preoperative HE4, CA125, and their combination in predicting recurrence was (86.4% *vs*. 72.7% *vs*. 90.9%), and the specificity was (100% *vs*. 85.7% *vs*. 100%). **Conclusion**: Serum HE4 combined with CA125 has a positive effect on the detection of EOC recurrence. To a certain extent,

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patients with higher preoperative HE4 and CA125 may face a higher risk of ovarian cancer recurrence.

【Key words】 Ovarian cancer; HE4; CA125; Recurrence; Epithelial ovarian cancer; Prediction; Diagnosis

卵巢癌(ovarian cancer, OC)是常见的妇科肿瘤,高居妇科恶性肿瘤致死率首位[1]。其中最常见的病理类型为上皮性卵巢癌(epithelial ovarian cancer, EOC),约占 OC 的 90%。由于缺乏典型的临床症状,使得卵巢癌早期诊断仍较困难,80% 以上病例确诊时已为晚期,5 年生存率仅为 29% ~35%,且约 70% 的患者出现术后复发[2-3],因此早期判别复发风险具有重要的临床意义。CA125 广泛用于 EOC 的疗效评估和复发监测[4-5],但特异性较差,亦可在其他良性疾病(如盆腔炎等)中异常表达[6],因此需与更具临床意义的标志物联合监测。具有较高特异性的血清生物标志物 HE4,被认为是较具有前景的新工具[7-9]。但关于 CA125 和 HE4 联合预测 EOC 复发的相关性研究较缺乏,预测术后复发的临床价值仍不明确,并且 OC 不同病理亚型的标志物表达水平存在较大差异,因此得出的结论尚不统一。本研究拟探讨减灭术前后不同时间点 HE4 联合 CA125 对于早期预测 EOC 复发的价值。

1　资料与方法

1.1　一般资料

选取 2017 年 7 月至 2022 年 7 月西南医科大学临床医学院收治的术后病检证实为 EOC 的患者作为研究对象,纳入标准:(1)接受了理想的肿瘤细胞减灭术,术后最大残留病灶 <1 cm;(2)术后病检证实为 EOC;(3)术后接受了以铂类为主的联合化疗;(4)术后进行规律随访,随访终点为因本病死亡或出现复发、截止至随访期;(5)完成术后 18 个月随访,且具有完整随访资料。排除标准:(1)合并其他系统的恶性肿瘤;(2)合并其他可能影响血清 CA125 和 HE4 数值的疾病;(3)病情未完全控制的患者;(4)失访或中途放弃治疗。

参考 2012 年美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)[10] 制定的复发标准,共纳入患者 50 例,分为复发组(22 例)及非复发组(28 例),所有复发患者均被证实有明确的影像学改变。

1.2　方法

于手术前、术后 1 个月、术后 3 个月、术后 6 个月,采集患者空腹肘静脉血 3 mL,以 3 000 r/min 离心 10 min 后将血清分离,使用日本东曹公司 AIA2000 电化学发光仪及试剂(罗氏 e601 型)测定血清 CA125,采用瑞士罗氏公司 Cobas 601 电化学发光仪测定血清 HE4。

1.3　统计学分析

采用 SPSS26.0 软件进行统计分析。计量资料符合正态分布的以($\bar{x} \pm s$)表示,组间比较采用独立样本 t 检验;偏态分布用[$M(P_{25}, P_{75})$]中位数和四分位数间距描述,使用非参数检验进行差异性分析;计数资料采用[n(%)]表示,组间比较采用独立样本 χ^2 检验。采用 Frideman 检验进行 HE4 和 CA125 组内不同时间点对比,采用 Mann-Whitney U 检验进行不同时间点 HE4、CA125、CA125/HE4 比值的组间对比;对术前 HE4 和 CA125 采用二元 Logistic 回归模型分析其与复发之间的关系,绘制受试者工作特征曲线(ROC)确定截断值,使用 MedCalc 软件对 ROC 曲线下面积(AUC)进行比较。$P<0.05$ 为差异有统计学意义。

2　结果

2.1　两组 EOC 患者临床与病理资料比较

两组患者的年龄、月经状况、病理学类型、病灶累及单侧或双侧、淋巴结转移情况、手术类型比较,差异均无统计学意义($P>0.05$);复发组国际妇产科联盟(International Federation of Gynecology and Obstetrics, FIGO)分期 Ⅲ - Ⅳ 期占比高于非复发组($P<0.05$)。见表 1。

表 1　两组患者临床病理资料比较[$\bar{x} \pm s$, n(%)]

资料	复发组(n=22)	非复发组(n=28)	χ^2/t 值	P 值
年龄	50.82 ± 6.960	51.29 ± 9.096	1.751	0.843
月经			0.063	0.802
绝经	11(50.00)	13(46.43)		
未绝经	11(50.00)	15(53.67)		
FIGO 分期			5.864	0.029
Ⅰ - Ⅱ	1(4.55)	9(32.14)		
Ⅲ - Ⅳ	21(95.45)	19(67.86)		
病理学类型			2.501	0.567
浆液性癌	16(72.73)	23(82.14)		
粘液性癌	2(9.09)	0(0.00)		
浆-粘液性癌	0(0.00)	2(7.14)		
透明细胞癌	4(18.18)	3(10.71)		
累及范围			1.155	0.283
单侧	10(45.45)	17(60.71)		
双侧	12(54.55)	11(39.29)		
淋巴结转移			0.192	0.661
有	12(54.55)	17(60.71)		
无	10(45.45)	11(39.29)		
手术类型			0.001	0.976
R0	18(81.82)	23(82.14)		
R1	4(18.18)	5(17.86)		

R0:肿瘤细胞减灭术完全切净肿瘤;R1:肿瘤细胞减灭术后单个残留肿瘤病灶最大径 1 cm。

2.2 两组各时间点 HE4、CA125 水平、CA125/HE4 水平比较

术前,复发组 HE4、CA125 水平均高于非复发组($P<0.05$),CA125/HE4 比值无统计学差异($P<0.05$)。术后 3 个月,复发组 HE4 水平低于非复发组,CA125/HE4 比值高于非复发组,差异有统计学意义($P<0.05$)。两组 HE4、CA125 在术后时间点均呈逐渐下降趋势($P<0.05$)。见表 2 及图 1。

表 2 两组不同时间点 HE4、CA125 水平、CA125/HE4 水平比较[$M(P_{25},P_{75})$]

指标	复发组($n=22$)	非复发组($n=28$)	Z 值	P 值
CA125(U/mL)				
术前	469.16 (300.25,649.81)	212.84(127.33,286.61)	-4.202	<0.001
术后 1 个月	97.12(44.95,178.46)	82.31(29.02,114.59)	-1.524	0.127
术后 3 个月	17.08(8.57,64.67)	10.30(6.40,16.02)	-1.881	0.060
术后 6 个月	6.73(3.96,24.49)	6.39(4.27,9.41)	-0.276	0.783
χ^2 值	63.818	76.671		
P 值	<0.001	<0.001		
HE4(pmol/L)				
术前	315.55(274.45,406.65)	129.50(82.63,183.18)	-5.590	<0.001
术后 1 个月	72.61(61.73,107.10)	69.84(58.79,81.16)	-1.212	0.226
术后 3 个月	64.89(51.60,99.33)	65.15(57.23,74.56)	-1.991	0.046
术后 6 个月	61.58(51.95,76.29)	56.16(47.22,69.36)	-0.704	0.482
χ^2 值	46.855	37.586		
P 值	<0.001	<0.001		
CA125/HE4				
术前	1.35(0.94,2.30)	1.57(0.95,2.65)	-0.332	0.740
术后 1 个月	1.17(0.75,1.75)	1.03(0.40,1.73)	-0.743	0.458
术后 3 个月	0.30(0.14,0.58)	0.16(0.10,0.24)	-2.463	0.014
术后 6 个月	0.12(0.67,0.28)	0.11(0.07,0.19)	-0.332	0.740
χ^2 值	45.327	64.414		
P 值	<0.001	<0.001		

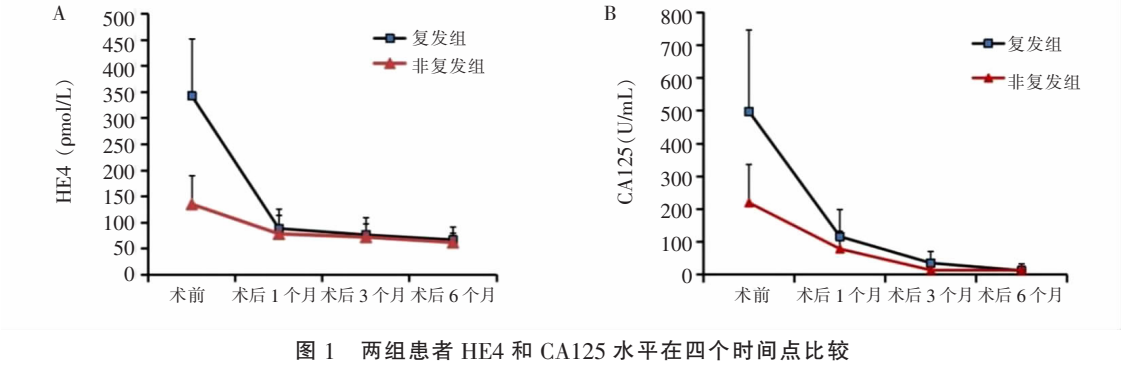

图 1 两组患者 HE4 和 CA125 水平在四个时间点比较

A. HE4; B. CA125

2.3 入组 EOC 患者复发的影响因素

将入组患者是否复发作为因变量,将表 1、表 2 中差异有统计学意义的指标作为自变量代入单因素 Logistic 回归模型分析。分析得出,FIGO 分期、术前 HE4、CA125 水平可能是 EOC 复发的危险因素($P<0.05$)。见表 3。

绘制术前 HE4、CA125 预测疾病复发的 ROC 曲线,*AUC* 分别为 0.964,95% *CI*(0.908 ~ 1.000);0.849,95% *CI*(0.742 ~ 0.956),二者比较差异无统计学意义($P>0.05$)。术前 HE4、CA125 预测疾病复发的最佳截断值为 254.62 pmol/L、330.85 U/mL,敏感度(86.4% *vs.* 72.7%),特异度(100% *vs.* 85.7%)。二者联合预测复发的 *AUC* 为 0.981,敏感度 90.9%,特异度 100%。见图 2。

表 3 入组 EOC 患者复发影响因素分析

变量	β 值	*SE* 值	*Wald* 值	*P* 值	*OR* (95% *CI*)
FIGO	2.297	1.101	4.357	0.037	9.947 (1.150 ~ 86.012)
术前 CA125	0.009	0.003	10.940	0.001	1.009 (1.004 ~ 1.015)
术前 HE4	0.036	0.110	11.440	0.001	1.037 (1.015 ~ 1.058)
术后 3 个月 HE4	0.005	0.010	0.295	0.587	1.006 (0.986 ~ 1.026)
术后 3 个月 CA125/HE4	-1.525	0.870	3.076	0.079	0.218 (0.040 ~ 1.196)

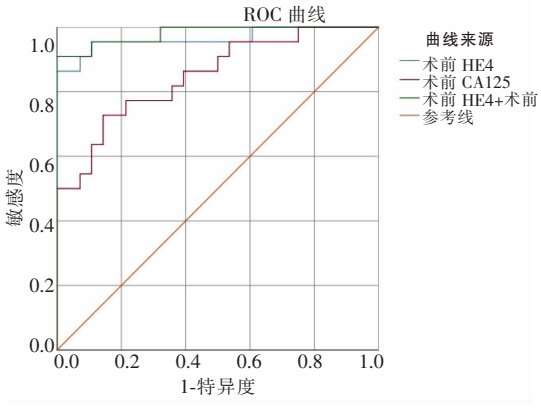

图 2　术前 CA125 和 HE4 水平与复发的 ROC 曲线

3　讨论

CA125 是一种糖蛋白,在 OC 患者疗效评估和复发监测等方面具有重要的临床价值[11]。尽管 CA125 常用作 EOC 复发监测的指标,但仍具有一定的局限性[12]。CA125 的表达增加可出现在除卵巢癌外的非妇科恶性肿瘤和各种良性疾病,如子宫内膜异位症、盆腔炎等[13]。因此需将 CA125 与更具有临床意义的标志物进行联合检测。HE4 最初发现于附睾远端上皮,尽管其在人体组织中分布广泛,但仅在病理组织中过度表达[14-15],不受月经期间激素波动的影响[16]。Innao 等[17]等研究发现 HE4 可预测卵巢癌复发,可能比 CA125 临床预测价值更高。

本研究结果显示,除 FIGO 分期外,术前 HE4、CA125 水平均可能是 EOC 复发的危险因素($P<0.05$),结论与 Ay 等[18]研究相符,二者处于高水平者可能面临较高的复发风险[19-21]。本研究还显示,进 HE4 在预测疾病复发的敏感度、特异度、*AUC* 等方面均优于 CA125,与既往研究[22]基本一致。当二者联合预测疾病复发时效果显著优于单独应用任一血清标志物[23-25]。另外,除术后 3 个月的 HE4 水平外,其余时间点 HE4、CA125 水平均为复发组高于非复发组($P>0.05$),表明 HE4、CA125 水平变化与疾病进展密切相关[26],术后 3 个月 HE4 水平可能与疾病复发相关($P<0.05$)。Steffensen 等[27]在 88 例 EOC 患者治疗后随访中发现,在随访的前 6 个月,CA125 的升高不是一个显著的预后因素,但 HE4 可能是疾病复发的敏感标志物,HE4 可弥补 CA125 的不足,但 CA125 无法补充 HE4 的预后价值。本研究发现,CA125/HE4 比值仅在术后 3 个月时间点差异具有统计学意义($P<0.05$),其余时间点均无统计学意义($P>0.05$)。进一步的回归分析提示术后 3 个月 CA125/HE4 比值也并非 EOC 复发的独立危险因素。CA125 的表达易受炎症、慢性肝病、肾病等影响,若入组患者在随访过程中合并上述疾病却并未被诊断,则 CA125/HE4 比值波动较大,进而影响检测结果的准确性。本研究还发现术后 3 个月时间点是一个重要的节点,尽管组间差异无统计学意义,但可能是由于样本量较小所致,后续需进行大样本量的多中心研究以进一步验证。

综上,术前及术后短期 HE4、CA125 对 EOC 术后复发具有一定的预测价值。患者血清 HE4 和 CA125 水平变化与 EOC 的发生发展密切相关。

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