doi: 10.13241/j.cnki.pmb.2024.18.011

血清 HE4、B7H4 表达水平及全身免疫炎症指数与卵巢癌患者临床病理特征及肿瘤转移的关系 *

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摘要 目的：探讨血清附睾蛋白 4(HE4)、B7 同源体 4(B7H4)表达水平及全身免疫炎症指数(SII)与卵巢癌患者临床病理特征及肿瘤转移的关系。**方法：**选取我院 2017 年 1 月到 2020 年 1 月收治的 80 例卵巢癌患者，将其分为恶性组，另选取同期 80 例良性卵巢病变患者分为良性组，80 名健康者作为对照组。对比三组受检者血清 HE4、B7H4 及 SII 表达水平。分析不同临床病理特征及肿瘤转移患者 HE4、B7H4 及 SII 表达水平，并采用 Spearman 相关性分析 HE4、B7H4 及 SII 与卵巢癌临床病理特征及肿瘤转移的相关性。并随访 3 年，记录总生存时间，分析 HE4、B7H4 及 SII 与卵巢癌生存期的关系。**结果：**三组患者 HE4、B7H4 及 SII 表达水平对比差异显著，恶性组明显高于良性组与对照组($P<0.05$)；不同年龄、组织学类型卵巢癌患者 HE4、B7H4 及 SII 表达水平对比无明显差异($P>0.05$)，不同 FIGO 分期、淋巴结转移、远处转移、肿瘤分化程度患者 HE4、B7H4 及 SII 表达水平对比差异显著($P<0.05$)；Spearman 相关分析结果表明，HE4、B7H4 及 SII 与卵巢癌组织学类型无明显相关性，与 FIGO 分期、淋巴结转移、远处转移及肿瘤分化程度呈正相关($P<0.05$)；所有患者进行 4 年随访，HE4 高水平患者中位总生存时间为 23.53(6.42~42.13)个月个月明显低于低水平患者中位总生存时间 32.54(14.53~42.13)个月。B7H4 高水平患者中位总生存时间为 21.32(6.42~42.13)个月明显低于低水平患者中位总生存时间 31.32(14.63~42.13)个月。SII 高水平患者中位总生存时间为 20.36(6.42~42.13)个月明显低于低水平患者中位总生存时间 34.68(13.56~42.13)个月($P<0.05$)。**结论：**血清 HE4、B7H4、SII 表达与卵巢癌临床分期、淋巴结转移、远处转移及肿瘤分化程度相关，且三者高表达可能意味着患者预后不良。

关键词：附睾蛋白 4；B7 同源体 4；全身免疫炎症指数；卵巢癌

中图分类号：R737.31 **文献标识码：**A **文章编号：**1673-6273(2024)18-3460-05

The Relationship between Serum HE4 and B7H4 Expression Levels, Systemic Immune Inflammation Index, Clinical Pathological Characteristics, and Tumor Metastasis in Ovarian Cancer Patients*

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ABSTRACT Objective: To investigate the expression levels of serum Epididymal protein 4 (HE4) and B7 homolog 4 (B7H4), as well as the relationship between systemic immune inflammation index (SII) and clinical pathological characteristics and tumor metastasis in ovarian cancer patients. **Methods:** 80 ovarian cancer patients admitted to our hospital from January 2017 to January 2020 were divided into malignant group, 80 patients with benign ovarian lesions in the same period were divided into benign group, and 80 healthy patients were selected as the control group. The serum expression levels of HE4, B7H4 and SII were compared in the three groups. The expression levels of HE4, B7H4 and SII in patients with tumor metastasis, and Spearman correlation between HE4, B7H4 and SII and the clinicopathological features of ovarian cancer and tumor metastasis. And followed up for 3 years, record the overall survival time, and analyze the relationship between HE4, B7H4 and SII and ovarian cancer survival. **Results:** There were differences in the expression levels of HE4, B7H4, and SII among the three groups of patients. The malignant group was significantly higher than the benign group and the control group ($P<0.05$); There was no difference in the expression levels of HE4, B7H4, and SII among ovarian cancer patients of different ages and histological types($P>0.05$). However, there were differences in the expression levels of HE4, B7H4, and SII among patients with different FIGO stages, lymph node metastasis, distant metastasis, and tumor differentiation degree ($P<0.05$); The Spearman correlation analysis results showed that HE4, B7H4, and SII were not significantly correlated with the histological type of ovarian cancer, but were positively correlated with FIGO staging, lymph node metastasis, distant metastasis, and tumor differentiation degree($P<0.05$); All patients were followed up for 4 years, and the median overall survival time of patients with high HE4 levels was 23.53 (6.42-42.13) months,

* 基金项目：陕西省自然科学基金项目(2023-JC-YB-807)

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（收稿日期：2024-02-06 接受日期：2024-02-28）

which was lower than that of patients with low HE4 levels, which was 32.54 (14.53-42.13) months. The median overall survival time of B7H4 high-level patients was 21.32 (6.42-42.13) months, which was lower than that of low-level patients at 31.32 (14.63-42.13) months. The median overall survival time of patients with high-level SII was 20.36 (6.42-42.13) months, which was lower than that of patients with low-level SII at 34.68 (13.56-42.13) months(P<0.05). **Conclusion:** Serum expression of HE4, B7H4 and SII are correlated with clinical stage of ovarian cancer, lymph node metastasis, distant metastasis and degree of tumor differentiation, and high expression of the three may mean poor prognosis of patients.

Key words: Epididymal protein 4; B7 homolog 4; Systemic immune inflammation index; Ovarian cancer

Chinese Library Classification(CLC): R737.31 Document code: A

Article ID: 1673-6273(2024)18-3460-05

前言

卵巢肿瘤是女性生殖系统常见肿瘤之一，发病率较高，多见于 40 岁以上女性[1]。卵巢肿瘤有良性与恶性之分，良性肿瘤多以成熟畸胎瘤、浆液性囊腺瘤等为主，恶性肿瘤以浆液腺囊腺癌、颗粒细胞瘤等为主，卵巢恶性肿瘤 5 年生存期为 25%~30%[2,3]。因此，早期识别，并诊断病情，对于改善卵巢癌患者预后具有重要价值。随着临床医疗技术发展，越来越多学者认为通过检测血清学指标对于诊断卵巢癌相关具有重要价值[4]。血清附睾蛋白 4(HE4)在肿瘤细胞异常增殖过程中表达量升高[5]。B7 同源体 4(B7H4)可对 T 淋巴细胞免疫功能产生抑制作用，降低 T 淋巴细胞对肿瘤细胞的吞噬能力和杀伤能力，造成肿瘤细胞免疫逃逸[6]。全身免疫炎症指数(SII)是对机体免疫和炎症状态的重要评价工具，研究发现[7,8]，在结直肠癌、生殖细胞肿瘤以及胃癌等预后中具有重要预测作用。因此，本研究探讨血清 HE4、B7H4 表达水平及全身免疫炎症指数与卵巢癌患者临床病理特征及肿瘤转移的关系。

1 资料与方法

1.1 一般资料

选取我院 2017 年 1 月到 2020 年 1 月收治的 80 例卵巢癌患者，将其分为恶性组，另选取同期 80 例良性卵巢病变患者分为良性组，80 名健康者作为对照组。恶性组年龄为 43~72 岁，平均年龄（54.32± 8.92）岁。良性组年龄为 42~72 岁，平均(54.28± 7.38)岁。对照组年龄为 45~70 岁，平均(54.27± 6.86)岁。本研究经我院伦理委员会批准。两组患者均为女性，且一般资料对比无明显差异(P>0.05)，具有可比性。

1.2 纳排标准

纳入标准：符合卵巢癌诊断标准[9]；临床资料完整；初诊卵巢癌者；均为女性；年龄≥18 岁；对本研究知情同意。

排除标准：合并其他恶性肿瘤患者；合并肝肾等重要脏器障碍者；近期使用过激素类药物治疗者；合并免疫功能障碍类疾病者；合并认知功能异常者；有卵巢手术史者；术后转移复发者；预计生存期≤3 个月者。

1.3 方法

血清 HE4、B7H4 及 SII 检测方法：抽取所有受检者清晨空腹静脉血 5 mL，应用 1500 r/min 的速度离心 15 min，取上层清液，应用全自动电化学发光免疫分析仪(型号：Cobase602)检测 HE4 表达水平，应用酶标仪(型号：DG5033A)检测 B7H4 表达水平，检测步骤严格依照试剂盒说明书进行。HE4 试剂盒由罗氏公司提供，B7H4 试剂盒由自南京伯斯金生物公司提供。取 HE4、B7H4 中位数值，将 HE4 水平≥140 pmol/L 判定为高水平，B7H4≥135 pmol/L 判定为高水平。并对所有患者进行空腹血常规检查，记录血小板、淋巴细胞、中性粒细胞计数，SII= 血小板 / 淋巴细胞比值（PLR）* 中性粒细胞计数，取 SII 中位数值，将 SII≥230 判定为高水平。

收集所有患者临床病理资料，其中包括年龄、FIGO 分期、组织学类型、淋巴结转移、远处转移、组织学分化程度等。并对所有患者进行 3 年随访，记录所有患者的总生存时间，分析 HE4、B7H4 及 SII 与卵巢癌生存时间的关系。

1.4 统计学方法

采取 SPSS 23.0，计数资料以(n/%)表示，x^2 检验；计量资料用($\bar{x}\pm s$)表示，t 检验或 F 检验；以 P<0.05 为差异有统计学意义。

2 结果

2.1 卵巢癌患者血清 HE4、B7H4 及 SII 表达水平分析

三组患者 HE4、B7H4 及 SII 表达水平对比差异显著，恶性组明显高于良性组与对照组(P<0.05)，如表 1 所示。

表 1 卵巢癌患者血清 HE4、B7H4 及 SII 表达水平分析($\bar{x}\pm s$)

Table 1 Analysis of serum expression levels of HE4, B7H4 and SII in ovarian cancer patients ($\bar{x}\pm s$)

Groups	n	HE4(pmol/L)	B7H4(pmol/L)	SII
Malignant group	80	235.77± 47.14	221.67± 54.24	319.63± 75.27
Benign group	80	46.64± 5.15	67.25± 11.16	186.25± 37.68
Control group	80	31.52± 6.17	51.96± 6.16	112.73± 22.79
F	-	65.724	16.746	25.647
P	-	0.001	0.001	0.001

2.2 不同临床病理特征卵巢癌患者 HE4、B7H4 及 SII 表达水平分析

不同年龄、组织学类型卵巢癌患者者 HE4、B7H4 及 SII 表达水平对比无明显差异($P>0.05$),不同 FIGO 分期、淋巴结转移、远处转移、肿瘤分化程度患者 HE4、B7H4 及 SII 表达水平对比差异显著($P<0.05$),如表 2 所示。

表 2 不同临床病理特征卵巢癌患者 HE4、B7H4 及 SII 表达水平分析($\bar{x}\pm s$)

Table 2 Analysis of the expression levels of HE4, B7H4 and SII in ovarian cancer patients with different clinicopathological characteristics($\bar{x}\pm s$)

Classification	n	HE4(pmol/L)	t/F	*P*	B7H4(pmol/L)	t/F	*P*	SII	t/F	*P*
Age										
＞50 Years old	34	234.85± 52.63	0.045	0.964	223.15± 44.26	0.519	0.605	321.78± 43.71	0.045	0.964
≤50 Years old	46	236.89± 31.13			221.68± 64.11			316.78± 52.43		
FIGO stage										
Ⅰ-Ⅱ stage	45	213.57± 45.78	6.900	0.001	218.85± 63.63	7.362	0.001	261.29± 57.42	5.455	0.001
Ⅲ-Ⅳ stage	35	265.37± 56.62			248.89± 64.13			353.19± 48.29		
Histological type										
Serous adenocarcinoma	52	235.79± 42.83	0.879	0.382	220.37± 63.62	0.241	0.867	320.30± 63.09	1.363	0.168
Endometrioid adenocarcinoma	18	238.32± 56.83			219.57± 59.78			324.47± 70.84		
Other	10	235.63± 57.36			224.53± 68.47			322.68± 65.83		
Lymphatic metastasis										
Yes	20	278.83± 48.25	11.253	0.001	250.79± 37.83	8.513	0.001	380.52± 67.73	7.894	0.001
No	60	202.83± 39.62			198.32± 56.83			245.02± 53.79		
Distance transfer										
Yes	17	282.77± 49.73	18.353	0.001	261.83± 45.25	13.567	0.001	392.57± 78.24	11.648	0.001
No	63	191.89± 42.27			179.83± 38.62			225.80± 63.82		
Degree of tumor differentiation										
Poorly differentiated	58	218.78± 56.43	7.262	0.001	207.77± 59.73	5.035	0.001	302.19± 76.24	6.372	0.001
Medium and high differentiation	22	253.78± 61.71			248.89± 57.27			340.23± 71.16		

2.3 HE4、B7H4 及 SII 与卵巢癌临床病理特征及肿瘤转移的相关性

Spearman 相关分析结果表明,HE4、B7H4 及 SII 与卵巢癌组织学类型无明显相关性,与 FIGO 分期、淋巴结转移、远处转移及肿瘤分化程度呈正相关($P<0.05$),如表 3 所示。

表 3 HE4、B7H4 及 SII 与卵巢癌临床病理特征及肿瘤转移的相关性

Table 3 Correlations of HE 4, B7H4 and SII with clinicopathological features of ovarian cancer and tumor metastasis

Groups	HE4		B7H4		SII	
	r	*P*	r	*P*	r	*P*
FIGO stage	0.579	0.012	0.457	0.020	0.636	0.008
Histological type	0.273	0.121	0.261	0.123	0.162	0.318
Lymphatic metastasis	0.657	0.007	0.414	0.024	0.626	0.008
Distance transfer	0.738	0.003	0.378	0.034	0.625	0.008
Degree of tumor differentiation	0.627	0.008	0.562	0.012	0.426	0.022

2.4 HE4、B7H4 及 SII 与卵巢癌生存期的关系

所有患者进行 4 年随访，HE4 高水平患者中位总生存时间为 23.53(6.42~42.13)个月个月明显低于低水平患者中位总生存时间 32.54(14.53~42.13)个月，如图 1 所示。B7H4 高水平患者中位总生存时间为 21.32(6.42~42.13)个月明显低于低水平患者中位总生存时间 31.32(14.63~42.13)个月，如图 2 所示。SII 高水平患者中位总生存时间为 20.36(6.42~42.13)个月明显低于低水平患者中位总生存时间 34.68(13.56~42.13)个月，如图 3 所示。

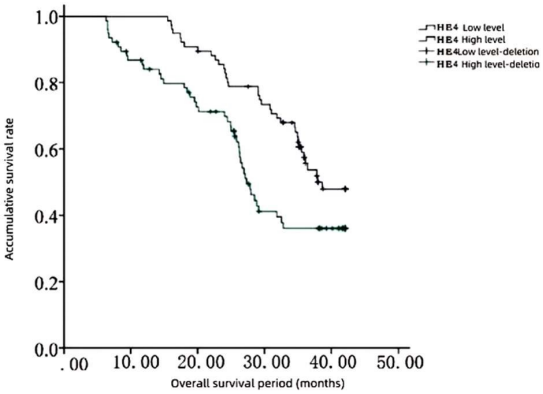

图 1 HE4 与卵巢癌生存期的关系

Fig.1 Association between HE 4 and ovarian cancer survival

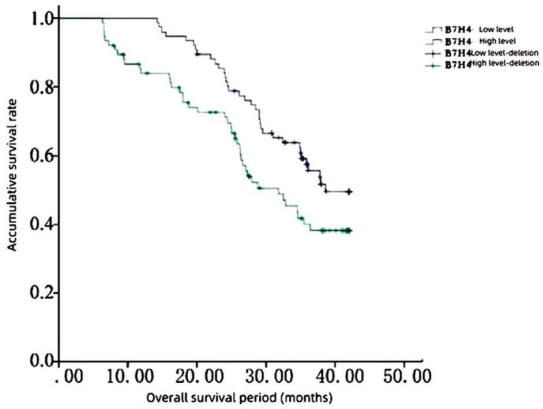

图 2 B7H4 与卵巢癌生存期的关系

Fig.2 B7H4 and ovarian cancer survival

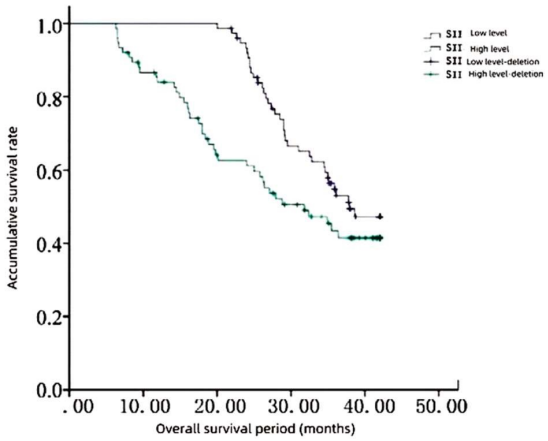

图 3 SII 与卵巢癌生存期的关系

Fig.3 Relationship between SII and ovarian cancer survival

3 讨论

卵巢作为女性重要的生殖器官，能够维持正常生殖功能、确保内分泌平衡、产生类固醇激素[10,11]。随着社会的不断发展，环境污染加剧，再加上饮食习惯和生活方式的改变，卵巢癌发病率逐年增加，严重影响女性身体健康。临床实践发现，卵巢癌患者在疾病早期并无显著临床症状与表现，许多患者在确诊时已经发展到了中晚期，需要采用化疗或者化疗联合手术等综合方案进行治疗，且预后较差[12-14]。因此，及时对卵巢癌进行精准评价及病情判断，尽早采取治疗措施进行干预，对提升患者生存质量具有重要价值。研究发现[15,16]，虽然部分卵巢癌女性通过手术、放化疗、靶向治疗等综合治疗方式有效改善了其预后水平，但针对部分远处转移及淋巴结转移患者疗效较差，且中位生存时间不足 1 年，还有部分患者在治疗早期就出现了疾病进展。本研究想通过本次研究为卵巢癌治疗及诊断提供一定思路。

本研究结果表明，三组患者 HE4、B7H4 及 SII 表达水平对比差异显著，恶性组明显高于良性组与对照组（$P<0.05$），与 Plotti F 等[17]、Chen X 等[18]、Zhou Y 等[19]研究结果相符。Plotti F 等研究显示，恶性肿瘤患者 HE4 水平呈现上升状态。分析原因为，HE4 主要表达于新生儿胚胎组织、神经阻滞及胚胎上皮组织之中，HE4 可经巯基结构作用于肿瘤糖蛋白分子激活，进而调节肿瘤相关信号通路，参与恶性肿瘤发生、发展[20]。Chen X 等研究显示，上皮性卵巢癌血清及组织中 B7H4 显著高于健康群体和良性卵巢肿瘤患者。分析原因为，B7H4 可负向调控免疫功能，抑制树突状细胞抗原能力，降低免疫应答水平[21]。Zhou Y 等研究发现，免疫状态和全身炎症与恶性肿瘤的发生与发展密切相关，炎症指标中例如降钙素原、C 反应蛋白、血小板、淋巴细胞以及中性粒细胞等与肿瘤的发生、发展及预后具有显著相关性[22]。但单项指标并不能准确的反应机体炎症反应状态，SII 将中性粒细胞、血小板及淋巴细胞结合，综合性评价机体炎症反应过程，可提升卵巢癌的诊断及预后评价价值[23]；不同年龄、组织学类型卵巢癌患者者 HE4、B7H4 及 SII 表达水平对比无明显差异（$P>0.05$），不同 FIGO 分期、淋巴结转移、远处转移、肿瘤分化程度患者 HE4、B7H4 及 SII 表达水平对比差异显著（$P<0.05$），与 Mao H 等[24]、Ahangar NK 等[25]研究结果部分一致。以往临床上针对 HE4、B7H4 及 SII 三者与卵巢癌的关系已有一定定论，但对于其与卵巢癌患者临床病理特征及肿瘤转移是否相关尚无确切定论。本研究发现，HE4、B7H4 及 SII 与卵巢癌组织学类型无明显相关性，与 FIGO 分期、淋巴结转移、远处转移及肿瘤分化程度呈正相关。分析可知：HE4、B7H4 病理生理途径相关。HE4 的高表达可反映卵巢上皮细胞核分裂速度，进而对癌细胞异常扩增风险进行评估[26]。但是 B7H4 表达水平升高会减少肿瘤细胞凋亡比例，影响免疫应答速度[27]。SII 的高表达相应的表明 PLT 与中性粒细胞表达量升高，淋巴细胞降低[28,29]。中性粒细胞所分泌的中性粒细胞外诱捕网除了可产生物理诱捕，杀死病原体之外，还可能与肿瘤的发生与发展密切相关[30]。最后本研究发现，HE4、B7H4 及 SII 高水平卵巢癌患者生存期明显低于低水平患者，B7H4 蛋白发挥负性调控并作用于 T 细胞增殖，所以 B7H4 过表达可能会导致肿瘤相关因子逃逸，导致肿瘤进展，缩短患者生存期[31]。

综上，血清 HE4、B7H4、SII 表达与卵巢癌临床分期、淋巴结转移、远处转移及肿瘤分化程度相关，且三者高表达可能意味着患者预后不良。

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