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# 血清 VEGF-A、sHLA-G、Syndecan-1 水平与子宫内膜异位症患者疾病分期和痛经程度的相关性及其联合检测的诊断价值研究\*

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**摘要目的:**探讨血清血管内皮生长因子-A(VEGF-A)、可溶性人类白细胞抗原-G(sHLA-G)、多配体蛋白多糖-1(Syndecan-1)水平与子宫内膜异位症(EMS)患者疾病分期和痛经程度的相关性及其联合检测的诊断价值。**方法:**选取2018年1月~2021年12月我院收治的120例EMS患者作为观察组,另取同期女性健康体检者120例作为对照组。检测并比较两组血清VEGF-A、sHLA-G、Syndecan-1水平。此外,分别对比不同疾病分期、不同痛经程度EMS患者上述三项指标水平的差异。采用Spearman相关系数分析血清VEGF-A、sHLA-G、Syndecan-1水平与疾病分期、痛经程度的相关性。以受试者工作特征(ROC)曲线分析上述三项指标联合检测对EMS的诊断效能。**结果:**观察组血清VEGF-A、sHLA-G、Syndecan-1水平均高于对照组( $P<0.05$ )。R-AFS分期为III~IV期的EMS患者其血清VEGF-A、sHLA-G、Syndecan-1水平均高于I~II期患者( $P<0.05$ )。痛经程度为中度和重度的EMS患者其血清VEGF-A、sHLA-G、Syndecan-1水平均高于轻度痛经患者,且重度痛经患者上述指标水平均高于中度痛经患者( $P<0.05$ )。Spearman相关性分析结果显示:EMS患者的血清VEGF-A、sHLA-G、Syndecan-1水平与疾病分期、痛经程度均呈正相关( $P<0.05$ )。ROC曲线分析结果显示:血清VEGF-A、sHLA-G、Syndecan-1联合检测诊断EMS的曲线下面积为0.894,明显高于三指标单独检测。**结论:**EMS患者血清VEGF-A、sHLA-G、Syndecan-1均存在异常高表达,且和疾病分期以及痛经程度有关,可能有助于临床EMS诊断及病情评估。

**关键词:**子宫内膜异位症;VEGF-A;sHLA-G;Syndecan-1;疾病分期;痛经程度;诊断价值

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## The Correlation between the Levels of Serum VEGF-A, sHLA-G, Syndecan-1 and Disease Stages and Dysmenorrhea Degree in Patients with Endometriosis and the Diagnostic Value Study of its Combined Detection\*

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**ABSTRACT Objective:** To investigate the correlation between the levels of serum vascular endothelial growth factor-A (VEGF-A), soluble human leukocyte antigen-G (sHLA-G), Syndecan-1 and the disease stages and dysmenorrhea degree in patients with endometriosis (EMS) and the diagnostic value of its combined detection. **Methods:** 120 patients with EMS who were treated in our hospital from January 2018 to December 2021 were selected as the observation group, and 120 female physical examiners in the same period were selected as the control group. The levels of serum VEGF-A, sHLA-G and Syndecan-1 were detected and compared between the two groups. In addition, the differences of the above three indexes in patients with EMS with different disease stages and different dysmenorrhea degree were compared. Spearman correlation coefficient was used to analyze the correlation between the levels of serum VEGF-A, sHLA-G and Syndecan-1 and disease stage and dysmenorrhea degree. Using receiver operating characteristic (ROC) curve to analyze the diagnostic efficiency of the above three indexes in the combined detection of EMS. **Results:** The levels of serum VEGF-A, sHLA-G and Syndecan-1 in the observation group were higher than those in the control group ( $P<0.05$ ). The levels of serum VEGF-A, sHLA-G and Syndecan-1 in patients with EMS with R-AFS stage III~IV were higher than those in patients with stage I~II ( $P<0.05$ ). The levels of serum VEGF-A, sHLA-G and Syndecan-1 in patients with EMS with moderate and severe dysmenorrhea were higher than those in patients with mild dysmenorrhea, and the levels of the above indexes in patients with severe dysmenorrhea were higher than those in patients with moderate dysmenorrhea ( $P<0.05$ ). Spearman correlation analysis showed that the levels of serum VEGF-A, sHLA-G and Syndecan-1 in patients with EMS were positively correlated with disease stage and dysmenorrhea degree ( $P<0.05$ ). ROC curve analysis showed that the area under the curve of serum VEGF-A, sHLA-G and Syndecan-1 in the diagnosis of EMS was 0.894, which was significantly higher than that of the three indexes alone. **Conclusions:** Serum VEGF-A, sHLA-G and Syndecan-1 in patients

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with EMS have abnormally high expression, which is related to disease stage and dysmenorrhea degree, which may be helpful for clinical EMS diagnosis and condition evaluation.

**Key words:** Endometriosis; VEGF-A; sHLA-G; Syndecan-1; Disease stage; Dysmenorrhea degree; Diagnostic value

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## 前言

子宫内膜异位症(EMS)属于女性生殖系统疾病之一,主要是因子宫内膜腺体以及间质异常种植于子宫腔之外导致的一组疾病。而 EMS 作为良性病变之一,其却有和肿瘤侵袭、转移相似的恶性行为,严重威胁患者的身心健康<sup>[1-3]</sup>。因此,如何有效早期诊断 EMS 并开展积极治疗显得尤为重要,亦是当下临床研究的热点。血管内皮生长因子-A(VEGF-A)属于一种促血管生成因子,可发挥提升微小静脉通透性的作用,继而导致细胞外基质异常改变以及纤维蛋白沉积,进一步为肿瘤血管生成、浸润、转移创造有利条件<sup>[4-6]</sup>。可溶性人类白细胞抗原-G(sHLA-G)主要参与了炎症以及肿瘤侵袭、转移等过程<sup>[7-9]</sup>。多配体蛋白多糖-1(Syndecan-1)主要介导了细胞分化表型维持以及细胞增殖、黏附等过程,目前已有报道证实其与多种恶性肿瘤生长、侵袭有关<sup>[10-12]</sup>。然而,有关上述三项指标与 EMS 的关系尚未完全阐明。本文通过研究上述三项血清学指标在 EMS 患者中的表达水平及与 EMS 患者疾病分期和痛经程度的相关性,并分析三项指标对 EMS 的诊断价值,以期为该病的诊断和病情评估提供新的靶点与思路,现作以下报道。

## 1 资料与方法

### 1.1 一般资料

选择 2018 年 1 月~2021 年 12 月我院收治的 120 例 EMS 患者作为观察组。纳入标准:(1)符合中华医学会《子宫内膜异位症的诊治指南》<sup>[13]</sup>中 EMS 的诊断标准,并经影像学检查确诊;(2)育龄期女性;(3)入组前未接受过相关治疗;(4)知情同意本研究。排除标准:(1)病情危重者;(2)合并自身免疫性疾病或恶性肿瘤者;(3)伴有心血管疾病或代谢性疾病者;(4)心、肝、肺等脏器功能严重障碍者;(5)生殖器官发育不良者;(6)合并精神疾病或认知障碍者。观察组年龄 24~48 岁,平均(35.92±6.23)岁;体重指数(BMI)19~32 kg/m<sup>2</sup>,平均(23.01±2.01)kg/m<sup>2</sup>;生育情况:已生育 75 例,未生育 45 例。另取我院同期女性健康体检者 120 例作为对照组,年龄 22~48 岁,平均

(35.88±6.17)岁;BMI 19~32 kg/m<sup>2</sup>,平均(23.15±2.03)kg/m<sup>2</sup>;生育情况:已生育 86 例,未生育 34 例。观察组与对照组上述一般资料对比无统计学差异( $P>0.05$ )。我院医学伦理委员会已批准本研究。

### 1.2 研究方法

(1)疾病分期:参考美国生育协会修订的 R-AFS 分期标准<sup>[14]</sup>对此次纳入研究的 120 例 EMS 患者进行分期,其中 I~II 期 61 例、III~IV 期 59 例。(2)痛经程度评估:采用视觉模拟评分法(VAS)<sup>[15]</sup>评估所有患者的痛经程度,VAS 总分 0~10 分,0 分为无痛,1~3 分为轻度疼痛,4~6 分为中度疼痛,7~10 分为重度疼痛。据此将此次纳入研究的 EMS 患者分为轻度 41 例、中度 40 例、重度 39 例。(3)血清 VEGF-A、sHLA-G、Syndecan-1 检测:采集所有受试者的晨起空腹静脉血 3 mL,离心处理(离心半径 10 cm,离心速率 3000 r/min,离心 10 min)后将上层血清保存在 -80℃冰箱中备用待测。采用酶联免疫吸附试验检测血清 VEGF-A、sHLA-G、Syndecan-1 水平,所有操作遵循试剂盒(上海酶联生物科技有限公司)说明书完成。

### 1.3 统计学方法

采用 SPSS 27.0 软件分析本研究所得数据,首先进行正态性与方差齐性检验,符合正态分布的计量资料以( $\bar{x}\pm s$ )表示,两组比较采用独立样本 t 检验,多组比较采用单因素方差分析。计数资料以例(%)表示,比较采用  $\chi^2$  检验。血清 VEGF-A、sHLA-G、Syndecan-1 水平与疾病分期、痛经程度的关系采用 Spearman 相关性分析。以受试者工作特征(ROC)曲线分析上述三项指标对 EMS 的诊断效能。 $P<0.05$  表示差异有统计学意义。

## 2 结果

### 2.1 观察组与对照组血清 VEGF-A、sHLA-G、Syndecan-1 水平对比

观察组血清 VEGF-A、sHLA-G、Syndecan-1 水平均高于对照组( $P<0.05$ ),见表 1。

表 1 观察组与对照组血清 VEGF-A、sHLA-G、Syndecan-1 水平对比( $\bar{x}\pm s$ )

Table 1 Comparison of the levels of serum VEGF-A, sHLA-G and Syndecan-1 between observation group and control group( $\bar{x}\pm s$ )

Groups	n	VEGF-A(pg/mL)	sHLA-G( $\mu$ g/L)	Syndecan-1( $\mu$ g/L)
Observation group	120	338.47±103.04	10.82±2.11	4031.23±413.89
Control group	120	56.12±10.30	5.43±1.40	1905.81±312.50
t	-	29.869	23.317	44.894
P	-	0.000	0.000	0.000

### 2.2 不同疾病分期 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 水平对比

R-AFS 分期为 III~IV 期的 EMS 患者其血清 VEGF-A、

sHLA-G、Syndecan-1 水平均高于 I~II 期患者( $P<0.05$ ),见表 2。

表 2 不同疾病分期 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 水平对比( $\bar{x}\pm s$ )

Table 2 Comparison of the levels of serum VEGF-A, sHLA-G and Syndecan-1 in patients with EMS at different disease stages( $\bar{x}\pm s$ )

R-AFS stages	n	VEGF-A(pg/mL)	sHLA-G( $\mu$ g/L)	Syndecan-1( $\mu$ g/L)
Stage I ~II	61	267.19 $\pm$ 89.45	8.45 $\pm$ 1.46	3125.29 $\pm$ 374.16
StageIII~IV	59	412.17 $\pm$ 112.06	13.27 $\pm$ 2.59	4967.88 $\pm$ 427.65
t	-	-7.846	-12.502	-25.143
P	-	0.000	0.000	0.000

2.3 不同痛经程度 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 水平对比  
sHLA-G、Syndecan-1 水平均高于轻度痛经患者,且重度痛经患者上述指标水平均高于中度痛经患者( $P<0.05$ ),见表 3。

痛经程度为中度和重度的 EMS 患者其血清 VEGF-A、

表 3 不同痛经程度 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 水平对比( $\bar{x}\pm s$ )

Table 3 Comparison of the levels of serum VEGF-A, sHLA-G and Syndecan-1 in patients with EMS with different dysmenorrhea degree( $\bar{x}\pm s$ )

Dysmenorrhea degree	n	VEGF-A(pg/mL)	sHLA-G( $\mu$ g/L)	Syndecan-1( $\mu$ g/L)
Mild	41	251.49 $\pm$ 76.23	8.71 $\pm$ 1.22	3235.10 $\pm$ 401.34
Moderate	40	340.31 $\pm$ 112.35 <sup>a</sup>	10.92 $\pm$ 2.08 <sup>a</sup>	4041.19 $\pm$ 438.53 <sup>a</sup>
Severe	39	423.19 $\pm$ 124.59 <sup>ab</sup>	12.94 $\pm$ 2.26 <sup>ab</sup>	4831.87 $\pm$ 472.39 <sup>ab</sup>
F	-	26.180	49.757	131.461
P	-	0.000	0.000	0.000

Note: compared with patients with mild dysmenorrhea, <sup>a</sup> $P<0.05$ . Compared with patients with moderate dysmenorrhea, <sup>b</sup> $P<0.05$ .

2.4 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 水平与疾病分期、痛经程度的相关性  
VEGF-A、sHLA-G、Syndecan-1 水平与疾病分期、痛经程度均呈正相关关系( $P<0.05$ ),见表 4。

Spearman 相关性分析结果显示:EMS 患者的血清

表 4 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 水平与疾病分期、痛经程度的相关性

Table 4 Correlation between serum the levels of VEGF-A, sHLA-G and Syndecan-1 and disease stage and dysmenorrhea degree in patients with EMS

Indexes	R-AFS stage		Dysmenorrhea degree	
	$r_s$	P	$r_s$	P
VEGF-A	0.393	0.000	0.384	0.000
sHLA-G	0.346	0.009	0.420	0.000
Syndecan-1	0.372	0.001	0.366	0.004

2.5 血清 VEGF-A、sHLA-G、Syndecan-1 联合检测对 EMS 的诊断价值  
can-1 单独及联合检测诊断 EMS 的 AUC(0.95CI)分别为 0.730 (0.508~0.952)、0.729 (0.532~0.915)、0.756 (0.581~0.927)、

ROC 曲线分析结果显示:血清 VEGF-A、sHLA-G、Syndecan-1 联合检测时诊断效能较高,见表 5、图 1。

表 5 血清 VEGF-A、sHLA-G、Syndecan-1 联合检测对 EMS 的诊断价值

Table 5 Diagnostic value of combined detection of serum VEGF-A, sHLA-G and Syndecan-1 in EMS

Indexes	AUC(0.95CI)	Threshold	Sensitivity(n/N)	Specificity(n/N)	Jordan index	Accuracy(n/N)
VEGF-A	0.730(0.508-0.952)	441.39 pg/mL	0.742(89/120)	0.717(86/120)	0.459	0.729(175/240)
sHLA-G	0.729(0.532-0.915)	12.56 $\mu$ g/L	0.717(86/120)	0.717(86/120)	0.434	0.717(172/240)
Syndecan-1	0.756(0.581-0.927)	4410.53 $\mu$ g/L	0.742(89/120)	0.758(91/120)	0.500	0.750(180/240)
Three joint	0.894(0.832-0.944)	-	0.875(105/120)	0.892(107/120)	0.767	0.883(212/240)

### 3 讨论

EMS 病变特点包括形态多样、局部浸润生长迅速、侵袭和

转移能力较强等,往往波及宫骶韧带以及卵巢等部位,会导致不同程度的痛经以及不孕,不但影响了患者的生存质量,而且会对家庭和产产生负面影响<sup>[10]</sup>。因此,如何早期有效诊断 EMS,

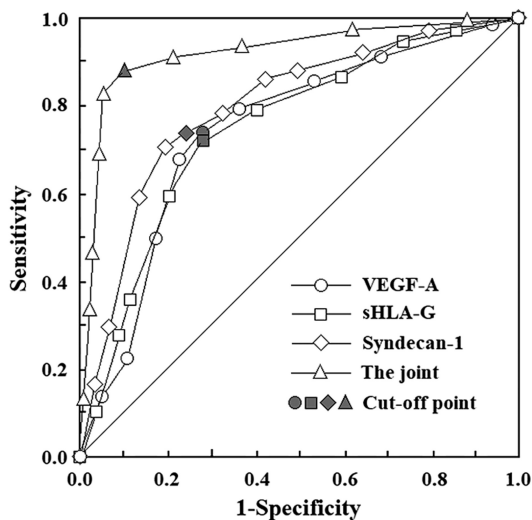


图1 血清 VEGF-A、sHLA-G、Syndecan-1 联合检测诊断 EMS 的 ROC 曲线

Fig.1 ROC curve of combined detection of serum VEGF-A, sHLA-G and Syndecan-1 in the diagnosis of EMS

并对患者病情严重程度进行评估显得尤为重要,亦是临床治疗方案制定、实施的重要依据<sup>[17,18]</sup>。目前腹腔镜检查仍是国际公认的 EMS 诊断的最佳方法,准确性较高<sup>[19,20]</sup>。然而,该诊断方式检查费用较高,且重复率较低,存在一定的局限性。因此,寻求和 EMS 发生、发展息息相关的生物学指标也一直是临床研究热点之一。

本文结果发现,观察组血清 VEGF-A、sHLA-G、Syndecan-1 水平均高于对照组。这提示了 EMS 患者血清 VEGF-A、sHLA-G、Syndecan-1 均存在异常高表达,三者可能在 EMS 的发生、发展过程中扮演了至关重要的角色。究其原因,可能是 VEGF-A 可促进血管网增生,进一步促进了异位内膜的种植以及生长,继而导致异位病灶的发生、发展、扩散<sup>[21,22]</sup>。sHLA-G 属于 MHC-I b 类抗原分子之一,主要是通过对自然杀伤(NK)细胞以及细胞毒性 T 淋巴细胞活性产生抑制作用,继而参与了肿瘤细胞的免疫逃逸,而 EMS 有着与肿瘤侵袭、转移非常相似的恶性行为,由此推测,sHLA-G 可能增强了 EMS 的异位内膜逃避机体免疫监视能力,进一步为其异位种植、生长提供重要基础<sup>[23,24]</sup>。Syndecan-1 胞外区通过 HS 链和细胞外基质分子、细胞因子以及细胞表面黏附分子等一系列配体相结合,继而实现细胞的黏附迁移、生长增殖以及新生血管形成等功能<sup>[25,26]</sup>。此外,R-AFS 分期为 III~IV 期的 EMS 患者其血清 VEGF-A、sHLA-G、Syndecan-1 水平均高于 I~II 期患者。这反映了随着 EMS 患者病情的加重,上述三项血清学指标水平升高。考虑原因,可能是 VEGF-A 是促血管作用最强的一种有丝分裂原,其在血管形成过程中发挥着中枢性调控作用,是关键性血管形成刺激因子,其表达水平的升高反映了新生血管形成的增加,继而导致病情加重<sup>[27,28]</sup>。sHLA-G 表达的升高促进了异位内膜细胞黏附、种植以及生长,从而对周围组织产生侵袭性破坏,致使病变的不断扩散并发生转移,继而导致了患者病情的加剧。Syndecan-1 水平的升高增加了 EMS 患者子宫内膜细胞异位黏附种植的成功率,继而促进了新生血管的形成,进一步促进了 EMS 病情的进展<sup>[29,30]</sup>。另外,痛经程度为中度和重度的 EMS 患

者其血清 VEGF-A、sHLA-G、Syndecan-1 水平均高于轻度痛经患者,且重度痛经患者上述指标水平均高于中度痛经患者。这提示了上述三项血清学指标水平的升高,EMS 患者的痛经程度加剧。分析原因,可能是随着血清 VEGF-A、sHLA-G、Syndecan-1 水平的升高,往往反映了患者病情的加剧,疾病对患者造成的影响势必增加,继而导致痛经程度显著。经 ROC 曲线分析发现,血清 VEGF-A、sHLA-G、Syndecan-1 联合检测诊断 EMS 的曲线下面积、灵敏度、特异度以及约登指数均高于上述三项指标单独诊断。这说明了联合检测上述三项血清学指标水平,可能对 EMS 的早期诊断具有一定的参考价值。其中主要原因可能是联合检测可为医生提供更为全面的依据,继而实现对疾病的准确诊断。

综上所述,血清 VEGF-A、sHLA-G、Syndecan-1 表达和 EMS 的发生、发展有关,联合检测可能有助于 EMS 的早期诊断,且可作为评估患者疾病分期以及痛经程度的可靠生物学指标。

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