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不同 FIGO 分期子宫内膜癌患者外周血红细胞分布宽度、血清对氧磷酶 -1 表达水平差异及其诊断价值分析 *

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摘要 目的:探讨不同国际妇产科学联合会(FIGO)分期子宫内膜癌患者外周血红细胞分布宽度(RDW)、血清对氧磷酶-1(PON-1)表达水平差异及其诊断价值。**方法:**选取我院 2018 年 1 月到 2020 年 1 月收治的 80 例子宫内膜癌患者作为研究对象,根据 FIGO 分期对所有患者进行分组,分为 I 期组 23 例,II 期组 22 例,III 期组 18 例,IV 期组 17 例。另选取同期来我院体检的 30 名健康志愿者作为对照组,对比所有受检者 RDW、PON-1 表达水平,并应用 ROC 曲线分析外周血红细胞分布宽度、血清对氧磷酶-1 表达水平对不同 FIGO 分期子宫内膜癌的诊断价值。对 80 例子宫内膜癌患者进行 2 年随访,将 2 年内死亡的 25 例患者分为死亡组,将其余 55 例患者分为存活组,对比死亡组与存活组临床一般情况与 RDW、PON-1 表达水平,并应用 logistic 回归分析分析 RDW、PON-1 对子宫内膜癌的预后预测价值。**结果:**五组受检者 RDW、PON-1 水平对比差异显著,IV 期组 RDW 水平高于 III 期组、II 期组、I 期组和对照组,IV 期组 PON-1 水平低于 III 期组、II 期组、I 期组和对照组($P<0.05$);RDW 结合 PON-1 联合诊断的准确度、敏感度、阳性预测值高于 RDW 单一诊断和 PON-1 单一诊断 ($P<0.05$)。RDW 诊断子宫内膜癌不同分期价值曲线下面积为 89.63,最佳诊断着色界限值为 75.73 %,PON-1 的曲线下面积为 78.89,最佳诊断着色界限值为 82.53 %,两者联合的曲线下面积为 84.26,最佳诊断着色界限值为 87.57 %;存活组与死亡组患者性别、年龄、病理类型对比无明显差异($P>0.05$),两组患者 FIGO 分期、基层浸润、组织分化程度、血清 RDW 与 PON-1 表达水平对比差异显著($P<0.05$);logistic 回归分析结果表明:基层浸润、RDW 与 PON-1 为子宫内膜癌患者预后的独立影响因素($P<0.05$)。**结论:**RDW、PON-1 联合对子宫内膜癌 FIGO 分期的诊断价值较高,且基层浸润、RDW 与 PON-1 为子宫内膜癌患者预后的独立影响因素。临床上需针对基层浸润、RDW 升高与 PON-1 水平降低的患者采取相关措施,改善治疗方案,降低患者死亡率情况。

关键词:FIGO 分期;子宫内膜癌;外周血红细胞分布宽度;对氧磷酶-1

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Analysis of the Differences in the Distribution Width of Peripheral Blood Red Blood Cells and the Expression Level of Serum Paraoxonase-1 in Patients with Endometrial Carcinoma at Different FIGO Stages and Their Diagnostic Value*

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ABSTRACT Objective: To investigate the difference of RDW and PON-1 expression in peripheral blood of patients with endometrial cancer in different FIGO stages and analyze their diagnostic value. **Methods:** 80 patients with endometrial cancer admitted to our hospital from January 2018 to January 2020 were selected as the study objects. All patients were divided into three groups according to FIGO stage: 23 patients in stage I group, 22 patients in stage II group, 18 patients in stage III group, and 17 patients in stage IV. In addition, 30 healthy volunteers who came to our hospital for physical examination at the same time were selected as the matched group to compare the expression levels of RDW and PON-1 of all subjects. The distribution width of peripheral red blood cells and the expression level of serum paraoxonase-1 were analyzed by using the ROC curve to determine the diagnostic value of endometrial cancer in different FIGO stages. 80 patients with endometrial cancer were followed up for two years. 25 patients who died within two years were divided into death group, and the remaining 55 patients were divided into survival group. The general clinical conditions, RDW and PON-1 expression levels in death group and survival group were compared. The prognostic value of RDW and PON-1 in endometrial cancer was ana-

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lyzed by logistic regression analysis. **Results:** The levels of RDW and PON-1 in five groups were different. The level of RDW in Phase IV group was higher than that in Phase III group, Phase II group, Phase I group and matched group, while the level of PON-1 in Phase IV group was lower than that in Phase III group, Phase II group, Phase I group and matched group ($P<0.05$); The accuracy, sensitivity and positive predictive value of combined diagnosis of RDW and PON-1 were higher than those of single diagnosis of RDW and PON-1 ($P<0.05$). The area under the value curve of different stages of endometrial cancer diagnosed by RDW was 89.63, the optimal diagnostic color limit value was 75.73 %, the area under the curve of PON-1 was 78.89, the optimal diagnostic color limit value was 82.53 %, the area under the curve of the combination of RDW and PON-1 was 84.26, and the optimal diagnostic color limit value was 87.57 %; There was no difference in sex, age and pathological type between the survival group and the death group ($P>0.05$). There was difference in FIGO stage, grassroots infiltration, tissue differentiation, serum RDW and PON-1 expression between the two groups ($P<0.05$); The above indicators with statistical differences in univariate analysis were assigned. The results of logistic regression analysis showed that grass-roots infiltration, RDW and PON-1 were independent prognostic factors for endometrial cancer patients ($P<0.05$). **Conclusion:** The combination of RDW and PON-1 has a high diagnostic value in FIGO staging of endometrial carcinoma, and grass-roots infiltration, RDW and PON-1 are independent prognostic factors of endometrial carcinoma. In clinical practice, relevant measures should be taken for patients with grass root infiltration, increased RDW and decreased PON-1 level to improve the treatment plan and reduce the mortality of patients.

Key words: FIGO staging; Endometrial carcinoma; Distribution width of peripheral red blood cells; Paraoxonase-1

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前言

子宫内膜癌是在子宫内膜腺体上发展的常见恶性肿瘤,其中绝经后和围绝经期女性发生率较高。当前子宫内膜癌的发生机制尚无明确定论,多数学者认为与过度肥胖、生活方式以及高血压病史等相关^[1]。子宫内膜癌根治术是早期患者常用的手术方式,具有创伤性小,术后并发症少等优点,同时再配合术后化疗,能够进一步抑制肿瘤组织转移、浸润与生长,更大概率的提升手术成功率,减少复发情况^[2]。然而,临床上许多子宫内膜癌患者症状较为隐晦,首次诊断可能已经发展到中晚期。因此,为了给子宫内膜癌患者制定有效的治疗方案,需对其分期情况进行判断,从而提升其临床疗效。当前临床上对于子宫内膜癌的分期多以国际妇产科学联合会(International Federation of Obstetrics and Gynecology, FIGO)分期为主,虽然辨别较为准确,但是需要结合患者各检查指标进行综合判断,诊断局限性较大^[3]。随着临床生物分子学研究进展加深,越来越多学者推荐采用血清相关指标辅助判断子宫内膜癌及其疾病发展情况。大量研究发现^[4,5],外周血红细胞分布宽度(Distribution width of peripheral red blood cells, RDW)、血清对氧磷酶-1(Serum paraoxonase-1, PON-1)与子宫内膜癌的发生发展具有一定关系,但是否能够判断患者分期情况,并预测其预后尚无明确定论。因此,本研究探讨了不同FIGO分期子宫内膜癌患者外周血红细胞分布宽度、血清对氧磷酶-1表达水平差异及其诊断价值,具体报道如下。

1 资料与方法

1.1 一般资料

选取我院2018年1月到2020年1月收治的80例子宫内膜癌患者作为研究对象,根据FIGO分期对所有患者进行分组,分为I期组23例,II期组22例,III期组18例,IV期组17例。另选取同期来我院体检的30名健康志愿者作为对照组。本

研究经我院伦理委员会批准。

纳入标准:术后病理诊断确诊为子宫内膜癌^[6];临床资料完整;所有患者对本研究知情并签署同意书;

排除标准:诊断前未接受过子宫内膜癌相关治疗,其中包括手术、放化疗和靶向治疗等;合并其他恶性肿瘤;临床资料不全和不愿配合研究者;合并营养不良、感染性、代谢性、严重重要脏器等疾病者。

1.2 方法

FIGO分期方法:根据FIGO分期,子宫内膜癌可以分为0~IV期,0期表示异常细胞局限于子宫内层表面,医学上也称为原位癌;I期表示肿瘤已经突破子宫内层,到达子宫内层;II期表示癌细胞已经侵袭子宫颈;III期表示肿瘤已经生长穿过子宫,侵袭附近组织,比如阴道、淋巴结等;IV期表示肿瘤已经侵袭膀胱或肠道,或者是癌细胞已经扩散至远处器官,比如肝脏、肺等。

RDW、PON-1检测方法:抽取清晨空腹肘静脉血液10 mL,以2000 r/s的速度离心15分钟,收集上层清液放置-70摄氏度的冰箱内待检。应用双夹心酶联免疫吸附法检测血清中PON-1表达水平,所用酶联免疫试剂盒均购置美国ZeptoMetrix公司,所有步骤严格按照说明书进行。并采集所有患者空腹静脉血2 mL,应用全自动血液分析仪(生产企业:希森美康公司;型号:XE9000)检测RDW水平。

对所有患者进行2年电话或上门随访,随访时间截止到2022年11月,记录80例子宫内膜癌患者2年内死亡情况。收集其一般临床资料,其中包括性别、年龄、病理类型、FIGO分期、基层浸润、组织分化程度、RDW、PON-1表达水平。

1.3 统计学方法

采取统计学软件SPSS 23.0对本研究数据进行分析,计数资料以例数/百分比(n/%)表示,进行 χ^2 检验;符合正态分布的计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,采用t检验;应用logistic回归分析分析上述RDW、PON-1对子宫内膜癌患者的

预后预测价值;应用 ROC 曲线评价 RDW、PON-1 对子宫内膜癌不同 FIGO 分期的诊断价值;以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 不同 FIGO 分期子宫内膜癌患者 RDW、PON-1 水平对比

表 1 不同 FIGO 分期子宫内膜癌患者 RDW、PON-1 水平对比

Table 1 Comparison of RDW and PON-1 levels in patients with endometrial cancer at different FIGO stages

Groups	n	RDW(%)	PON-1(kU/L)
Phase I group	23	17.59± 3.78	83.24± 15.34
Phase II group	22	21.76± 3.89	69.07± 10.36
Phase III group	18	25.21± 4.42	67.30± 8.57
Phase IV group	17	39.14± 6.34	54.19± 13.29
Matched group	30	15.64± 2.91	125.72± 33.87
F	-	96.582	45.245
P	-	<0.001	<0.001

2.2 RDW、PON-1 对子宫内膜癌不同分期的诊断价值

RDW 结合 PON-1 联合诊断的准确度、敏感度、阳性预测值高于 RDW 单一诊断和 PON-1 单一诊断 ($P<0.05$)。如表 2 所示。RDW 诊断子宫内膜癌不同分期价值曲线下面积为

五组受检者 RDW、PON-1 水平对比差异显著, IV 期组 RDW 水平高于 III 期组、II 期组、I 期组和对照组, IV 期组 PON-1 水平低于 III 期组、II 期组、I 期组和对照组 ($P<0.05$), 如表 1 所示。

89.63, 最佳诊断着色界限值为 75.73 %, PON-1 的曲线下面积为 78.89, 最佳诊断着色界限值为 82.53 %, 两者联合的曲线下面积为 84.26, 最佳诊断着色界限值为 87.57 %。如表 2 级图 1 所示。

表 2 RDW、PON-1 对子宫内膜癌不同分期的诊断价值

Table 2 Diagnostic value of RDW and PON-1 in different stages of endometrial carcinoma

Groups	Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value
RDW	95.00%(76/80)	87.50%(70/80)	75.00%(6/8)	72.50%(58/72)	66.67%(10/15)
PON-1	82.50%(66/80)	68.75%(55/80)	62.50%(5/8)	59.94%(41/72)	50.00%(16/32)
Combination of the two	98.75%(79/80)	100.00%(80/80)	87.50%(7/8)	97.22%(70/72)	82.61%(18/23)
χ^2	15.780	31.780	1.330	34.64	4.700
P	<0.001	<0.001	0.5134	<0.001	0.096

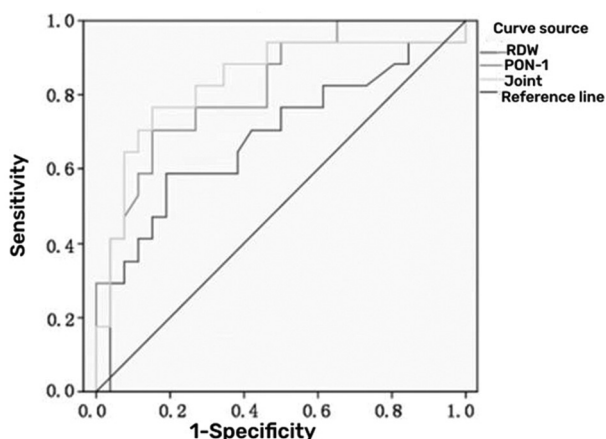


图 1 RDW、PON-1 对子宫内膜癌不同分期诊断的 ROC 曲线图

Fig.1 ROC Curve of RDW and PON-1 in Diagnosis of Endometrial Carcinoma at Different Stages

2.3 存活组与死亡组临床一般情况与 RDW、PON-1 表达水平

存活组与死亡组患者性别、年龄、病理类型对比无差异

($P>0.05$), 两组患者 FIGO 分期、基层浸润、组织分化程度、血清 RDW 与 PON-1 表达水平对比差异显著 ($P<0.05$), 如表 3 所示。

2.4 RDW、PON-1 表达水平对子宫内膜癌患者的预后预测价值

对上述单因素分析具有统计学差异的指标进行赋值, lo-gistic 回归分析结果表明:基层浸润、RDW 与 PON-1 为子宫内膜癌患者预后的独立影响因素 ($P<0.05$), 如表 4 所示。

3 讨论

RDW 是红细胞体积异质性的主要参数, 能进一步反应体内炎症环境、异常红医保和红细胞生成障碍情况, 以往临床上多采用 RDW 来诊断贫血情况^[7,8]。随着临床医学发展, 有研究发现^[9], RDW 是预测死亡敏感的独立相关因素, 近年来有研究发现, 外周血 RDW 对于诊断喉癌、卵巢癌以及肺癌等疾病具有重要价值, 但是否能够诊断子宫内膜癌与 FIGO 分期并无研究明确表明。血清对氧磷酶家族共包括 PON-1、PON-2 和 PON-3 3 个主要基因, 位于人体 7 号染色体长臂上, 其中

表 3 存活组与死亡组临床一般情况与 RDW、PON-1 表达水平

Table 3 General clinical conditions and expression levels of RDW and PON-1 in survival group and death group

Category	Survival group(n=55)	Death group(n=25)	χ^2/t	<i>P</i>
Gender				
Male	33	14	0.113	0.736
Female	22	11		
Age				
≥50 years old	36	16	0.016	0.899
<50 years old	19	9		
Pathological type				
Plasma breast cancer or clear cell cancer	35	15	0.097	0.755
Endometrioid endometrial carcinoma	20	10		
FIGO staging				
Phase I - II	38	7	11.792	0.001
Phase III - IV	17	18		
Base course infiltration				
<50 %	15	15	7.855	0.005
>50 %	40	10		
Tissue differentiation degree				
Low differentiation	30	9	8.235	0.016
Mesodifferentiation	17	5		
Highly differentiated	8	11		
RDW(%)	18.02± 3.79	29.47± 5.84	8.981	<0.001
PON-1(kU/L)	78.52± 15.73	56.30± 9.09	7.954	<0.001

表 4 RDW、PON-1 表达水平对子宫内膜癌患者的预后预测价值

Table 4 Prognostic value of RDW and PON-1 expression levels in patients with endometrial carcinoma

Factors	Parameter estimate	Standard error	Wald	<i>P</i>	OR	95% CI
FIGO staging	0.635	0.108	10.484	0.108	0.464	0.210~1.347
Base course infiltration	0.463	0.096	8.096	0.023	2.546	1.364~3.475
Tissue differentiation degree	0.847	0.304	13.274	0.124	0.747	0.314~1.249
RDW	0.464	0.105	8.484	0.016	2.774	1.876~4.010
PON-1	0.457	0.089	8.145	0.030	2.458	1.359~3.257

PON-1 术后 3 个成员中研究最多的一个,属于高密度脂蛋白相关酯酶的一种,亲脂性较为强烈^[10,11]。PON-1 表达与活性主要受到 PON-1 基因单核苷酸多态性影响^[12]。研究发现^[13-15],PON-1 与黄斑变性、肝脏、肾脏疾病、脑卒中、各种肿瘤、动脉粥样硬化以及糖尿病等多种疾病相关,同时 PON-1 基因多态性对不同种族之间也存在一定差异。Thompson EW 等^[16]研究发现,PON-1 在乳腺癌患者血清中浓度及活性较低,在健康人群中活性及浓度较高,但与子宫内膜癌患者 FIGO 分期的关系尚无明确定论。

本研究结果表明,五组受检者 RDW、PON-1 水平对比差异显著,IV 期组 RDW 水平明显高于 III 期组、II 期组、I 期组和对

照组,IV 期组 PON-1 水平明显低于 III 期组、II 期组、I 期组和对照组($P<0.05$)。由此证明,RDW、PON-1 水平与子宫内膜癌与 FIGO 分期具有明显关系,与袁利等^[17]和 Morris G 等^[18]研究相似。袁利等研究发现,子宫内膜癌合并 HPV 感染患者机体 RDW 水平明显升高,且不同肿瘤分期患者中,其分期越高 RDW 表达水平越高。这是因为,RDW 是反应红细胞大小一致性的相关参数,RDW 水平越高代表红细胞体积大小的离散性更大,若机体发生炎症变化,RDW 也随之升高^[19]。有研究发现^[20],肿瘤为慢性炎症结果,炎症细胞因子会对促红细胞生成素对于骨髓干细胞刺激作用产生抑制,从而在细胞成熟和抗细胞凋亡

过程中起到重要作用,导致许多没有成熟的红细胞被释放到机体外周血循环之中,增加 RDW 特异性,因此 RDW 升高与慢性炎症导致的无效造血具有一定关系。Morris G 等研究发现,子宫内膜癌患者血清 PON-1 的活性与其疾病程度与代谢综合征等相关指标具有一定联系。这可能是因为,当 PON-1 的活性降低达到一定水平后,细胞内外蛋白氧化毒性会累积一定数量,导致细胞增殖与分化发生变化,进而表达出无线增殖的恶性肿瘤特征。另外,可能与子宫内膜癌分期越高体内炎症状态越显著,从而对 PON-1 活性产生一定影响^[21]。

本研究结果显示,RDW 结合 PON-1 联合诊断的准确度、敏感度、阳性预测值明显高于 RDW 单一诊断和 PON-1 单一诊断($P<0.05$)。RDW 诊断子宫内膜癌不同分期价值曲线下面积为 89.63,最佳诊断着色界限值为 75.73 %,PON-1 的曲线下面积为 78.89,最佳诊断着色界限值为 82.5 3%,两者联合的曲线下面积为 84.26,最佳诊断着色界限值为 87.57 %。由此证明,RDW 结合 PON-1 联合诊断子宫内膜癌啊分期的效能更高,与 Kemal Y 等^[22]和 Sigal GA 等^[23]研究相符。这可能是因为,随着子宫内膜癌患者病情的发展,会出现造血原料不足和消化功能吸收障碍等症状,而肿瘤组织自身出血也会导致患者出现慢性失血情况,造成患者出现贫血或贫血前期症状,随着患者肿瘤分期增加,RDW 值也随之升高^[24]。另外据研究显示^[25],子宫内膜癌相关的肿瘤细胞因子和白细胞介素等因子升高,能够导致 PON-1 活性降低,这主要是因为子宫内膜癌患者体内 PON-1 会作为一种内源性自由基清除的重要系统之一,其活性受损也是导致患者抗氧化防御系统受损的一项重要原因,机体出现过氧化所导致的损伤同时还会对 PON-1 产生反作用,导致其活性降低,进而在子宫内膜癌患者体内形成恶性循环状态。因此,通过 RDW 结合 PON-1 联合诊断能够进一步通过不同机理提升子宫内膜癌不同分期的诊断效能。存活组与死亡组患者性别、年龄、病理类型对比无明显差异($P>0.05$),两组患者 FIGO 分期、基层浸润、组织分化程度、血清 RDW 与 PON-1 表达水平对比差异显著($P<0.05$),与侯俊芳等^[26]、Cetin 等^[27]、豆秋彦等^[28]研究相符。侯俊芳等研究发现,子宫内膜癌患者 FIGO 分期、基层浸润、组织分化程度越其死亡率越高,其临床特征能够预测子宫内膜癌患者死亡率。Cetin 等研究发现,RDW 水平与子宫内膜癌的发展具有一定关系,但是否对其预后具有预测价值尚无明确定论。豆秋彦等研究也发现,原发性子宫内膜癌血清 PON-1 活性降低,且多与 Q192R 基因多态性具有一定关系;logistic 回归分析结果表明:基层浸润、RDW 与 PON-1 为子宫内膜癌患者预后的独立影响因素($P<0.05$),与 Li X 等^[29]研究不符。Li X 等研究发现,RDW 虽然与肝内胆管癌具有一定关系,但并不属于其预后独立因素。本研究结果发现,PON-1 为子宫内膜癌预后相关指标,与韩利平等^[30]研究相符。韩利平等研究发现,PON-1 与水平变化与非肌层浸润性膀胱癌患者术后疾病转归具有明显关联性,可作为疾病转归监测手段,为临床治疗提供指导依据。

综上所述,RDW、PON-1 联合对子宫内膜癌 FIGO 分期的诊断价值较高,且基层浸润、RDW 与 PON-1 为子宫内膜癌患者预后的独立影响因素。临床上需针对基层浸润、RDW 升高与 PON-1 水平降低的患者采取相关措施,改善治疗方案,降低患

者死亡率情况。

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