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膜性肾病患者抗磷脂酶 A2 受体抗体定量水平与肾损伤标志物的相关性*

黄 宇¹,付美珍²,戴淑惠¹,李 珣^{1△}

1. 厦门大学附属第一医院检验科/厦门市基因检测重点实验室,福建厦门 361000;
2. 福建省龙岩市第一医院生殖医学科,福建龙岩 364000

摘 要:目的 探讨膜性肾病(MN)患者抗磷脂酶 A2 受体(PLA2R)抗体定量水平与肾损伤标志物的相关性。**方法** 回顾性选取 2020 年 5 月至 2021 年 4 月就诊于厦门大学附属第一医院的 79 例 MN 患者作为 MN 组。另选取同期 45 例临床诊断非 MN 患者作为对照组。比较两组抗 PLA2R 抗体定量水平的差异及不同截断值下的诊断性能。收集 MN 组血清和尿液标志物检测结果,包括尿液 24 h 尿蛋白(24 h-UTP)、尿微量清蛋白(ALB)与肌酐(Cr)比值(ACR)以及血清总蛋白(TP)、ALB、尿素氮(BUN)、Cr、半胱氨酸蛋白酶抑制剂胱抑素 C(Cys C)水平。根据改善全球肾脏病预后组织(KDIGO2012)指南以抗 PLA2R 抗体定量 150 RU/mL 为截断值分成低浓度组(≤ 150 RU/mL)和高浓度组(> 150 RU/mL),分析比较各肾损伤标志物差异。绘制受试者工作特征(ROC)曲线评价诊断效能。采用 Spearman 相关分析抗 PLA2R 抗体水平与 24 h-UTP、ACR、ALB、BUN 的相关性。**结果** MN 组抗 PLA2R 抗体水平[79.80(21.70,206.70)RU/mL]高于对照组[1.54(1.36,1.74)RU/mL],差异有统计学意义($Z = -8.47, P < 0.01$)。 < 40 岁、 $40 \sim 60$ 岁、 > 60 岁抗 PLA2R 抗体水平分别为 40.9(21.4,84.9)RU/mL、73.2(5.1,202.5)RU/mL、171.6(40.9,460.2)RU/mL,抗 PLA2R 抗体水平随年龄升高而升高,差异有统计学意义($H = 10.44, P < 0.05$)。截断值 ≥ 20 RU/mL 时,抗 PLA2R 抗体诊断 MN 的特异度为 100.0%,但灵敏度仅 78.5%。ROC 曲线分析结果显示,最佳截断值为 2.16 RU/mL 时,灵敏度为 92.4%,特异度为 95.6%,约登指数为 0.880。高浓度组纳入 27 例患者,低浓度组纳入 52 例患者。高浓度组 24 h-UTP、ACR、BUN 水平明显高于低浓度组,ALB 水平明显低于低浓度组,差异均有统计学意义($P < 0.05$)。Spearman 相关分析结果显示,抗 PLA2R 抗体与 24 h-UTP、ACR、BUN 呈正相关($r = 0.635、0.628、0.240, P < 0.05$),与 ALB 呈负相关($r = -0.344, P < 0.05$)。**结论** 抗 PLA2R 抗体定量水平对于 MN 患者具有较好诊断价值,抗 PLA2R 抗体定量水平与肾损伤标志物存在一定相关性,研究结果为本地区 MN 的临床诊断治疗提供参考。

关键词:膜性肾病; 抗磷脂酶 A2 受体抗体; 蛋白尿; 24 h 尿蛋白; 尿微量清蛋白与肌酐比值
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Correlation between quantitative level of anti-phospholipase A2 receptor antibody and markers of renal injury in patients with membranous nephropathy*
HUANG Yu¹,FU Meizhen²,DAI Shuhui¹,LI Xun^{1△}

1. Department of Clinical Laboratory,the First Affiliated Hospital of Xiamen University/Xiamen Key Laboratory of Genetic Testing,Xiamen,Fujian 361000,China; 2. Department of Reproductive Medicine,the First Hospital of Longyan City,Longyan,Fujian 364000,China

Abstract: Objective To investigate the correlation between the quantitative level of anti-phospholipase A2 receptor (PLA2R) antibody and renal injury markers in patients with membranous nephropathy (MN). **Methods** A total of 79 MN patients admitted to the First Affiliated Hospital of Xiamen University from May 2020 to April 2021 were retrospectively selected as the MN group. A total of 45 patients with clinically diagnosed non-MN during the same period were selected as the control group. The difference of anti-PLA2R antibody quantitative levels between the two groups and the diagnostic performance under different cut-off values were compared. The results of serum and urine markers in MN group were collected,including 24 h urinary protein (24 h-UTP),urinary albumin (ALB) to creatinine (Cr) ratio (ACR),and serum total protein (TP),albumin (ALB),blood urea nitrogen (BUN),Cr and cysteine protease inhibitor cystatin C (Cys C) levels. According to the guidelines of Kidney Disease:Improving Global Outcomes (KDIGO2012),the patients were divided into low concentration group (≤ 150 RU/mL) and high concentration group (> 150 RU/mL) according to the

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作者简介:黄宇,男,副主任技师,主要从事感染免疫相关方面的研究。 △ 通信作者,E-mail:xunlixmu@sina.com。

cut-off value of anti-PLA2R antibody 150 RU/mL. The differences of renal injury markers were analyzed and compared. The receiver operating characteristic (ROC) curve was drawn to evaluate the diagnostic efficiency. Spearman correlation analysis was used to analyze the correlation between anti-PLA2R antibody level and 24 h-UTP, ACR, ALB and BUN. **Results** The level of anti-PLA2R antibody in MN group [79.80 (21.70, 206.70) RU/mL] was higher than that in control group [1.54 (1.36, 1.74) RU/mL], and the difference was statistically significant ($Z = -8.47, P < 0.01$). The levels of anti-PLA2R antibody in <40 years old, 40–60 years old and >60 years old were 40.9 (21.4, 84.9) RU/mL, 73.2 (5.1, 202.5) RU/mL and 171.6 (40.9, 460.2) RU/mL, respectively. The level of anti-PLA2R antibody increased with age, and the difference was statistically significant ($H = 10.44, P < 0.05$). When the cut-off value was ≥ 20 RU/mL, the specificity of anti-PLA2R antibody in the diagnosis of MN was 100.0%, but the sensitivity was only 78.5%. The results of ROC curve analysis showed that the optimal cut-off value was 2.16 RU/mL, the sensitivity was 92.4%, the specificity was 95.6%, and the Youden index was 0.880. Twenty-seven patients were included in the high concentration group, and 52 patients were included in the low concentration group. The levels of 24 h-UTP, ACR and BUN in the high concentration group were significantly higher than those in the low concentration group, while the level of ALB was significantly lower than that of the low concentration group ($P < 0.05$). Spearman correlation analysis showed that anti-PLA2R antibody was positively correlated with 24 h-UTP, ACR and BUN ($r = 0.635, 0.628, 0.240, P < 0.05$), and negatively correlated with ALB ($r = -0.344, P < 0.05$). **Conclusion** The quantitative level of anti-PLA2R antibody has a good diagnostic value for patients with MN, and there is a certain correlation between the quantitative level of anti-PLA2R antibody and renal injury markers. The results provide a reference for the clinical diagnosis and treatment of MN in this area.

Key words: membranous nephropathy; anti-phospholipase A2 receptor antibody; proteinuria; 24 h urine protein; urinary albumin to creatinine ratio

膜性肾病(MN)是一种自身免疫性肾小球疾病,是导致成人肾病综合征的主要病因,其中大部分为特发性膜性肾病^[1-2]。肾组织 M 型磷脂酶 A2 受体(PLA2R)及其血清中的特异性抗体的发现和相关研究,促进了临床对膜性肾病发病机制、诊断与治疗的认识^[3-5]。抗 PLA2R 抗体在膜性肾病中的临床价值,与疾病活动性指标的相关性是当前研究的热点之一^[6-8]。肾病患者的病情评估通常依赖于肾功能指标,包括尿蛋白(UTP)、血清清蛋白(ALB)、肌酐(Cr)等。不同地区报道的抗 PLA2R 抗体水平与肾功能指标的相关性存在一定差异^[9-10],因此,需要更多临床资料的积累以进一步阐明其内在联系。本研究回顾收集厦门大学附属第一医院膜性肾病患者的临床资料数据,并分析抗 PLA2R 抗体定量水平与各肾损伤标志物的相关性,以期为本地区膜性肾病的临床诊断治疗提供参考,现报道如下。

1 资料与方法

1.1 一般资料 回顾性选取 2020 年 5 月至 2021 年 4 月就诊于厦门大学附属第一医院的 79 例 MN 患者作为 MN 组,其中男 53 例,女 26 例;年龄 23~92 岁,平均(53.4±14.9)岁。纳入标准:符合膜性肾病临床诊断标准^[11];有抗 PLA2R 抗体定量检测结果且资料齐全;入院前无激素、免疫抑制剂治疗史。排除标准:合并有严重感染性疾病、高血压、心脏病、糖尿病或系统性红斑狼疮患者。另选取同期 45 例临床诊断非 MN 患者作为对照组,其中男 27 例,女 18 例;年龄

20~78 岁,平均(49.2±14.8)岁;包括狼疮性肾炎、过敏性紫癜肾炎、糖尿病性肾病、高血压性肾病等。本研究通过本院医学伦理委员会审核批准。

1.2 方法 收集研究对象基本资料及抗 PLA2R 抗体定量检测结果,尿液 24 h 尿蛋白(24 h-UTP)、尿 ALB 与尿 Cr 的比值(ACR)、血清尿素氮(BUN)、Cr、胱抑素 C(Cys C)、总蛋白(TP)、ALB 等结果。抗 PLA2R 抗体定量采用 ELISA 法检测(欧蒙诊断);其他标志物检测采用仪器,测定试剂盒如下:尿 24 h-UTP 及尿 ACR(重庆博士泰);血清 BUN、Cr、TP、ALB(迈克生物);Cys C(北京利德曼)。分析比较不同性别、年龄(<40 岁、40~60 岁、 >60 岁)抗 PLA2R 抗体水平。评价抗 PLA2R 抗体定量的诊断性能。根据改善全球肾脏病预后组织(KDIGO2012)指南以抗 PLA2R 抗体定量 150 RU/mL 为截断值分成低浓度组(≤ 150 RU/mL)和高浓度组(>150 RU/mL)^[11],分析比较各肾损伤标志物差异。

1.3 统计学处理 采用 SPSS25.0 统计软件进行数据处理与统计分析。符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用独立样本 t 检验。计数资料以例数或百分率表示,组间比较采用 χ^2 检验。不符合正态分布的计量资料以 $M(P_{25}, P_{75})$ 表示,两组间比较采用 Mann-Whitney U 检验,多组间比较采用 Kruskal-Wallis H 检验。绘制受试者工作特征(ROC)曲线评价诊断效能。采用 Spearman 相关分析抗 PLA2R 抗体水平与 24h-UTP、ACR、ALB、BUN

的相关性。以 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 抗 PLA2R 抗体浓度水平比较 MN 组抗 PLA2R 抗体水平[79.80(21.70,206.70)RU/mL]高于对照组[1.54(1.36,1.74)RU/mL],差异有统计学意义($Z=-8.47, P<0.01$)。MN 组男性、女性抗 PLA2R 抗体定量水平分别为 79.8(20.9,200.5)RU/mL、107.0(24.5,345.1)RU/mL。 <40 岁、 $40\sim60$ 岁、 >60 岁抗 PLA2R 抗体水平分别为 40.9(21.4,84.9)RU/mL、73.2(5.1,202.5)RU/mL、171.6(40.9,460.2)RU/mL,抗 PLA2R 抗体水平随年龄升高而升高,差异有统计学意义($H=10.44, P<0.05$)。

2.2 抗 PLA2R 抗体定量水平的诊断性能 截断值 ≥ 20 RU/mL 时,抗 PLA2R 抗体诊断 MN 的特异度为 100%,但灵敏度仅 78.5%。ROC 曲线分析结果显示,最佳截断值为 2.16 RU/mL 时,灵敏度为 92.4%,特异度为 97.3%,约登指数为 0.880。见

表 1。

表 1 不同抗 PLA2R 抗体定量水平的诊断效能						
截断值 (RU/mL)	灵敏度 (%)	特异度 (%)	阴性预测 值(%)	阳性预测 值(%)	约登指数	<i>P</i>
≥ 2.00	92.4	86.7	86.7	92.4	0.791	<0.05
≥ 2.16	92.4	95.6	87.7	97.3	0.880	<0.05
≥ 14.00	79.7	100.0	73.8	100.0	0.797	<0.05
≥ 20.00	78.5	100.0	72.6	100.0	0.785	<0.05

2.3 低浓度组与高浓度组肾损伤标志物水平比较 高浓度组纳入 27 例患者,低浓度组纳入 52 例患者。抗 PLA2R 抗体高浓度组 24 h-UTP、ACR、BUN 水平明显高于低浓度组,ALB 水平明显低于低浓度组,差异均有统计学意义($P<0.05$);两组 TP、Cr、Cys C 水平比较,差异无统计学意义($P>0.05$)。见表 2。

表 2 低浓度组与高浓度组肾损伤标志物水平比较[$M(P_{25}, P_{75})$]

组别	<i>n</i>	24 h-UTP(mg/24 h)	ACR(mg/g)	TP(g/L)
低浓度组	52	2 259.00(906.00,5 214.00)	1 053.00(506.00,3 169.00)	52.00(44.10,58.30)
高浓度组	27	6 773.00(5 541.00,10 621.00)	3 756.00(2 012.00,5 046.00)	45.70(38.60,57.90)
<i>Z</i>		-4.083	-3.577	-1.463
<i>P</i>		<0.001	<0.001	0.144

组别	<i>n</i>	ALB(g/L)	BUN(mmol/L)	Cr(umol/L)	Cys C(mg/L)
低浓度组	52	28.30(22.60,32.70)	5.88(4.32,7.91)	80.00(61.00,99.00)	0.95(0.88,1.20)
高浓度组	27	20.50(18.30,30.10)	7.59(5.62,9.26)	81.00(66.00,97.00)	1.09(0.97,1.30)
<i>Z</i>		-2.14	-2.47	-0.372	-1.773
<i>P</i>		0.032	0.013	0.710	0.076

2.4 抗 PLA2R 抗体水平与 24 h-UTP、ACR、ALB、BUN 的相关性 Spearman 相关分析结果显示,抗 PLA2R 抗体与 24 h-UTP、ACR、BUN 呈正相关($r=0.635、0.628、0.240, P<0.05$),与 ALB 呈负相关($r=-0.344, P<0.05$)。

3 讨 论

MN 是成人肾病综合征常见病理类型之一。近年研究显示 PLA2R 抗原与血清抗 PLA2R 抗体在 MN 发病机制中起重要作用^[12-13]。抗 PLA2R 抗体能够特异结合肾小球上的磷脂酶 A2 受体形成免疫复合物,通过激活补体引起足细胞损伤,最终导致蛋白尿的产生。研究表明,血清抗 PLA2R 抗体出现在 70% 的特发性 MN 患者中,因此成为近 10 年关于特发性 MN 研究领域的热点^[14-16]。本研究结果提示 MN 组抗 PLA2R 抗体水平为明显高于非 MN 组。目前国内关于血清抗 PLA2R 抗体水平在患者性别、年龄相关的研究报道仍有限。本研究分析结果提示 MN 组男性、女性抗 PLA2R 抗体定量水平分别为 79.8(20.9,

200.5)RU/mL、107.0(24.5,345.1)RU/mL;按年龄分组显示抗 PLA2R 抗体水平随年龄升高($P<0.05$)。也有报道显示 MN 患者体内抗 PLA2R 抗体水平在不同的性别、年龄无明显差异,这可能与不同地区疾病人群构成差异相关。

有研究发现,血清抗 PLA2R 抗体在特发性 MN 诊断中具有较高的特异度和灵敏度,能够在一定程度上反映疾病活动程度^[17-18]。本研究分析了不同截断值下抗 PLA2R 抗体定量的诊断性能,当截断值 ≥ 20 RU/mL 时,抗 PLA2R 抗体诊断 MN 的特异度达 100.0%,但灵敏度仅 78.5%。ROC 曲线分析结果显示最佳截断值为 2.16 RU/mL,此时灵敏度 92.4%,特异度为 95.6%,约登指数达 0.880。蛋白尿是临床常见的肾损伤表现,患者肾小球受到损害后,自身机体功能失调,滤过屏障发生异常,出现蛋白尿^[19-20]。随着病情的不断进展,肾脏功能受损严重时会出现肾衰竭而危及患者生命。本研究以抗 PLA2R 抗体定量 150 RU/mL 为截断值分成低浓度组和高浓度组,分

析比较两组间各肾损伤标志物的差异。结果显示,抗 PLA2R 抗体高浓度组尿液标志物中的 24 h-UTP、ACR 值水平明显高于低浓度组。这与其他类似研究结果一致^[21]。高浓度的抗体水平伴随着病变局部大量抗原抗体复合物沉积,这些免疫复合物作用于肾小球基底膜上,激活补体系统形成大量膜攻击复合物,破坏了肾小球滤过屏障,从而导致蛋白尿^[13]。高浓度组血清 BUN 水平明显高于低浓度组,在一定程度上提示肾前性炎症反应,特别是肾小球的炎症程度。另外,高浓度组的 ALB 水平低于低浓度组,说明由于肾屏障破坏导致的血清清蛋白丢失;其他指标 TP、Cr、Cys C 等指标在两组间未显示明显差异。在进一步的相关性分析提示抗 PLA2R 抗体水平与 24 h-UTP、ACR、BUN 水平存在正相关关系($P < 0.05$),而与 ALB 呈负相关($P < 0.05$)。为本地区 MN 的临床诊治提供了重要参考依据。

本研究也存在一些局限性,如纳入分析的样本量较小,研究对象仅来自于单一医疗机构,仅对目标患者人群进行分析,未纳入对照人群更多资料进行比较;未采集详细临床资料,结合疾病的严重程度及患者预后等进行分析,且未对患者临床治疗监测抗 PLA2R 抗体水平进行动态观察,这些因素都将可能导致研究结果的偏倚,影响研究结论的普适性。今后有待完善样本资料做进一步研究。

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D-二聚体、25-羟维生素 D、乳酸、降钙素原联合检测对
脓毒血症患者预后的评估价值*

杜晓敏,戴科芳,张瑞英,刘 洁,蒋海燕

河北省邢台市第三医院重症医学科,河北邢台 054000

摘要:目的 探讨 D-二聚体(D-D)、25-羟维生素 D[25(OH)D]、乳酸(LA)、降钙素原(PCT)联合检测对脓毒血症患者预后的评估价值。方法 选取 2018 年 1 月至 2021 年 3 月在邢台市第三医院治疗的 116 例脓毒血症患者作为研究对象。根据急性生理与慢性健康状况系统(APACHE II)评分将患者分为 A、B、C 组,比较各组患者 D-D、25(OH)D、LA 及 PCT 水平。根据患者 28 d 生存情况将患者分为生存组与死亡组,比较两组 D-D、25(OH)D、LA 及 PCT 水平。采用 Pearson 相关分析脓毒症患者 D-D、25(OH)D、LA 及 PCT 水平与 APACHE II 评分的相关性。绘制受试者工作特征(ROC)曲线分析 D-D、25(OH)D、LA、PCT 单独及 4 项指标联合检测对脓毒症患者死亡的预测价值。结果 A 组 27 例患者,B 组 59 例患者,C 组 30 例患者,3 组 D-D、PCT、LA 水平比较,均为 A 组<B 组<C 组,差异均有统计学意义($P<0.05$)。3 组 25(OH)D 水平比较,A 组>B 组>C 组,差异均有统计学意义($P<0.05$)。生存组纳入 73 例患者,死亡组纳入 43 例患者。死亡组 D-D、LA、PCT 水平与 APACHE II 评分均高于生存组,25(OH)D 水平低于生存组,差异均有统计学意义($P<0.05$)。Pearson 相关分析结果显示,D-D、LA、PCT 水平与 APACHE II 评分均呈正相关($r=0.694,0.715,0.668,P<0.05$),25(OH)D 水平与 APACHE II 评分呈负相关($r=-0.603,P<0.05$)。ROC 曲线分析结果显示,D-D、25(OH)D、LA、PCT 对脓毒症患者死亡预测的曲线下面积分别为 0.901、0.891、0.803、0.759,均低于 4 项指标联合检测的 0.952($Z=3.715,3.692,4.039,5.156,P<0.05$)。结论 D-D、25(OH)D、LA、PCT 均对脓毒血症患者 28d 死亡具有较高的预测价值,且联合检测可提高诊断效能,可通过检测上述指标预测脓毒血症患者预后并指导治疗。

关键词:D-二聚体; 25-羟维生素 D; 乳酸; 降钙素原; 脓毒症; 预后

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Prognostic value of combined detection of D-dimer, 25-hydroxyvitamin D, lactic
acid and procalcitonin in patients with sepsis*

DU Xiaomin, DAI Kefang, ZHANG Ruiying, LIU Jie, JIANG Haiyan

Department of Critical Care Medicine, Xingtai Third Hospital, Xingtai, Hebei 054000, China

Abstract: Objective To investigate the value of combined detection of D-dimer (D-D), 25-hydroxyvitamin D[25(OH)D], lactic acid (LA) and procalcitonin (PCT) in evaluating the prognosis of patients with sepsis. **Methods** A total of 116 patients with sepsis treated in the Third Hospital of Xingtai from January 2018 to March 2021 were selected as the research objects. According to the acute physiology and chronic health evaluation II (APACHE II) score, the patients were divided into group A, B and C, and the levels of D-D, 25(OH)D, LA and PCT in each group were compared. According to the 28-day survival, the patients were divided into survival group and death group, and the levels of D-D, 25(OH)D, LA and PCT were compared between the two groups. Pearson correlation analysis was used to analyze the correlation between D-D, 25(OH)D, LA, PCT levels and APACHE II score in patients with sepsis. The receiver operating characteristic (ROC) curve was drawn to analyze the predictive value of D-D, 25(OH)D, LA, PCT alone and combined detection of the four indicators for the death of patients with sepsis. **Results** There were 27 patients in group A, 59 patients in group B and 30 patients in group C. The levels of D-D, PCT and LA in the three groups were compared, and all of them were group A < group B < group C, and the differences were statistically significant ($P<0.05$). The 25(OH)D level of the three groups was group A > group B > group C, and the differences were statistically significant ($P<0.05$). There were 73 patients in the survival group and 43 patients in the death group. The

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作者简介:杜晓敏,女,主治医师,主要从事脓毒症方面的研究。