

doi: 10.3978/j.issn.2095-6959.2019.05.006

View this article at: <http://dx.doi.org/10.3978/j.issn.2095-6959.2019.05.006>

血清 YKL-40 水平与多肌炎 / 皮肤炎的相关性

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[摘要] 目的: 探究血清YKL-40水平与多肌炎/皮肤炎(polymyositis/dermatomyositis, PM/DM)的相关性。方法: 纳入99例确诊为PM/DM患者和87例健康者(对照组)。ELISA检测血清YKL-40水平, 记录患者临床相关指标。以肌病活动性视觉模拟评分评估疾病的活动性, 以发生间质性肺病(interstitial lung disease, ILD)评估疾病的严重程度。结果: PM/DM患者血清YKL-40水平显著高于对照组, 差异有统计学意义。血清YKL-40水平与视觉模拟评分($r=0.65$, $P<0.01$)、C反应蛋白($r=0.33$, $P<0.01$)、红细胞沉降率($r=0.65$, $P<0.01$)、铁蛋白($r=0.62$, $P<0.01$)呈正相关。PM/DM患者中合并ILD患者血清YKL-40水平显著高于非ILD患者, 差异有统计学意义。YKL-40可用于评估ILD的诊断(ROC曲线下面积为0.82, $P<0.01$)。结论: 血清YKL-40水平可用于评估PM/DM的疾病活动性和严重程度。

[关键词] 多肌炎; 皮肤炎; YKL-40; 相关性

Correlation between serum YKL-40 and polymyositis/dermatomyositis

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Abstract **Objective:** To investigate the correlation between serum YKL-40 and polymyositis/dermatomyositis (PM/DM). **Methods:** A total of 99 patients with definite PM/DM were prospectively enrolled. 87 healthy individuals were set as a control. Serum YKL-40 levels were determined using ELISA. The clinical characteristics of PM/DM were recorded. Disease activity of PM/DM was estimated using myositis disease activity assessment visual analogue scale. Disease severity was estimated by the occurrence of interstitial lung disease (ILD). **Results:** The patients with PM/DM had significantly higher serum YKL-40 concentrations than the healthy controls. Serum YKL-40 levels were positively correlated with myositis disease activity assessment visual analogue scale ($r=0.65$, $P<0.01$), C-reactive protein ($r=0.33$, $P<0.01$), erythrocyte sedimentation rate ($r=0.65$, $P<0.01$) and ferritin ($r=0.62$, $P<0.01$). Patients with ILD had significantly higher YKL-40 concentrations than those without. The area under receiver operating characteristic curve of YKL-40 for identifying ILD was 0.87 ($P<0.01$). **Conclusion:** Serum YKL-40 is a useful biomarker for estimating disease activity or severity of PM/DM.

Keywords polymyositis; dermatomyositis; YKL-40; correlation

收稿日期 (Date of reception): 2018-12-04

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多肌炎/皮肌炎(polymyositis/dermatomyositis, PM/DM)是一种自身免疫功能异常介导的炎症性疾病, 主要累及骨骼肌、皮肤^[1]。其特征主要表现为自身抗体和肌肉酶的高表达, 骨骼肌炎性细胞大量浸润^[2]。骨骼肌的大量炎性细胞释放细胞因子和细胞毒性物质, 引起肌肉损伤^[3]。因此评估PM/DM的活动度和严重程度具有重要意义。间质性肺病(interstitial lung disease, ILD)是PM/DM的常见并发症, 常用于评估疾病的严重程度^[4]。临床上对于ILD的诊断主要依赖高分辨率CT(high-resolution computed tomography, HRCT)实现, 但检测费用昂贵, 临床上难以普及。此外一些生物标志物可用于评估PM/DM的活动度, 如B细胞活化因子^[5]、白介素-35^[6]、CD163^[7]等。但是这些因子需要联合检测, 且诊断价值有限^[8]。故找寻有效的诊断PM/DM疾病状态的生物标志物具有重要的临床意义。

YKL-40又名人类软骨糖蛋白-39(HCgp-39), 主要来源于人类软骨细胞、巨噬细胞、中性粒细胞等^[9-10]。近年研究^[11]表明: YKL-40在炎症反应的细胞增殖、迁移、分化及组织重塑等病理过程中发挥重要的作用。YKL-40的过表达与炎症性疾病的发病机制相关, 如心血管疾病^[12]、肿瘤^[13]、自身免疫性疾病。此外, YKL-40可用于评估自身免疫性疾病(如炎症性肠病^[14]、系统性红斑狼疮^[15]、类风湿性关节炎^[16])的活动度和严重程度。但YKL-40与PM/DM是否具有相关性, 目前还不清楚。因此本研究旨在探究YKL-40与PM/DM的相关性, 为临床诊断疾病提供理论依据。

1 对象与方法

1.1 对象

纳入2016年2月至2018年2月于恩施土家族苗族自治州中心医院门诊诊断为PM/DM的患者99例以及年龄、性别相匹配的体检健康人群87例(对照组)。患者均签署知情同意书。本研究获得恩施土家族苗族自治州中心医院医学伦理委员会审批。PM/DM诊断标准: 参考Bohan与Peter于1975年提出的诊断标准^[17]。排除标准: 患有其他自身免疫性疾病; 恶性肿瘤性疾病; 终末期肾脏病; 患有乙型肝炎; 1个月内发生感染性疾病。

1.2 观察指标

疾病活动度标准采用肌病活动性视觉模拟量表评分(myositis disease activity assessment visual

analogue scale, MYOACT)^[18]。疾病严重性标准: ILD疾病的发生。使用HRCT诊断ILD。其他观察指标: 年龄、性别、PM/DM病程、C反应蛋白、红细胞沉降率、肌酸激酶、乳酸脱氢酶、铁蛋白。

1.3 统计学处理

采用SPSS 19.0统计软件进行数据分析。计数资料采用均数±标准差($\bar{x}\pm s$)表示, 连续变量使用t检验或U检验; 分类变量使用卡方检验; 对于血清YKL-40水平与多个参数的相关性使用Pearson相关性分析; 绘制ROC曲线, 计算曲线下面积(AUC)等评价指标的诊断效能。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 纳入对象的一般情况

PM/DM组与对照组相比, 年龄、性别之间无明显统计学差异($P>0.05$)。PM/DM组患者血清C反应蛋白、红细胞沉降率、肌酸激酶、乳酸脱氢酶、铁蛋白水平较对照组显著升高, 差异有统计学意义($P<0.05$, 表1)。

2.2 血清 YKL-40 水平

PM/DM组患者血清YKL-40水平显著高于对照组[(57.4±7.8) g/L vs (27.4±5.5) μg/L], 差异有统计学意义($P<0.01$, 图1)。

2.3 血清 YKL-40 水平与 PM/DM 患者相关临床指标的相关性

进一步分析血清YKL-40与PM/DM患者临床相关指标的相关性, 结果如图1所示, ILD患者血清YKL-40水平显著高于非ILD患者[(76.5±10.8) μg/L vs (42.5±8.1) μg/L], 差异有统计学意义($P=0.02$)。

此外, 对YKL-40水平进行相关性分析发现: YKL-40水平与MYOACT、C反应蛋白、红细胞沉降率、铁蛋白呈正相关(均 $P<0.01$, 表2)。

2.4 血清 YKL-40 水平可作为诊断 ILD 的生物标志物

由于ILD患者血清YKL-40水平显著高于非ILD患者, 因此进一步探讨YKL-40能否作为诊断ILD的生物标志物。通过ROC曲线分析发现, YKL-40诊断ILD的AUC为0.87(95% CI: 0.79~0.95, $P<0.01$), 敏感度为0.91, 特异性为0.67, 临界值为56.8 μg/L(图2)。

表1 纳入对象的一般特征

Table 1 General characteristics of the included subjects

组别	<i>n</i>	年龄/岁	性别/(男/女)	PM/DM/例	病程/月	MYOACT
PM/DM组	99	65.3 ± 10.2	67/32	58/41	8.7 ± 2.3	5.4 ± 1.3
对照组	87	59.6 ± 8.6	57/30	—	—	—
<i>P</i>		0.22	0.76	—	—	—

组别	ILD/例	C反应蛋白/ (mg·L ⁻¹)	红细胞沉降率/ (mm·h ⁻¹)	肌酸激酶/ (U·L ⁻¹)	乳酸脱氢酶/ (U·L ⁻¹)	铁蛋白/ (ng·mL ⁻¹)
PM/DM组	23	12.4 ± 2.4	36.4 ± 5.6	379.6 ± 56.4	403.1 ± 75.3	345.3 ± 54.2
对照组	—	2.3 ± 0.4	6.5 ± 1.4	45.3 ± 12.3	155.4 ± 40.8	189.5 ± 50.2
<i>P</i>	—	0.01	0.04	0.03	0.02	0.01

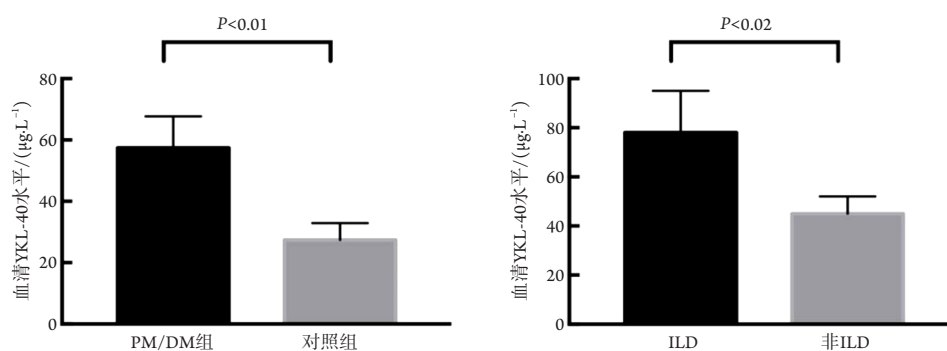


图1 各组患者血清YKL-40水平

Figure 1 Serum YKL-40 levels among each group

表2 YKL-40相关的变量分析

Table 2 Correlation analysis about YKL-40

参数	<i>r</i>	<i>P</i>
MYOACT	0.65	<0.01
C反应蛋白	0.33	<0.01
红细胞沉降率	0.65	<0.01
肌酸激酶	0.38	0.16
乳酸脱氢酶	0.25	0.12
铁蛋白	0.62	<0.01

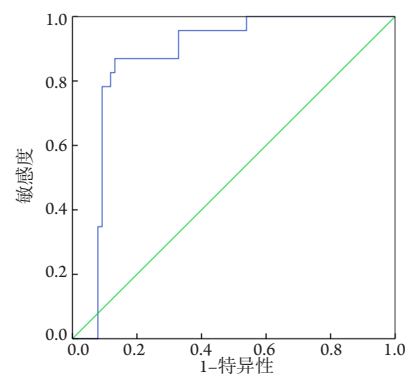


图2 YKL-40诊断ILD的ROC曲线

Figure 2 Receiver operator characteristic curve about YKL-40 for detecting interstitial lung disease

3 讨论

YKL-40是一种炎症相关因子,在许多炎症性疾病中高表达^[19]。有研究^[20]证实YKL-40与C反应蛋白具有正相关性。此外,YKL-40被证实是一些炎症相关性疾病(如脑卒中^[21]、肿瘤^[22]等)的危险因素。对健康志愿者注射内毒素^[23]或者炎症细胞因子^[24]后,循环YKL-40水平显著升高。本研究中,PM/DM患者血清YKL-40水平显著高于对照组。因此血清YKL-40水平与PM/DM具有相关性。PM/DM患者血清YKL-40水平升高的原因目前并不十分清楚,可能与巨噬细胞(YKL-40的主要来源细胞之一)激活有关。研究^[25]发现:PM/DM患者体内单核巨噬细胞激活,导致循环中YKL-40的水平升高。体外研究^[26]也发现激活巨噬细胞能促进YKL-40的表达。但是具体机制仍有待更深一步研究。

本研究还发现YKL-40与MYOACT、C反应蛋白、铁蛋白、红细胞沉降率呈正相关,提示YKL-40可作为评估PM/DM活动度的生物标志物。ILD是PM/DM常见的严重并发症,与疾病的严重程度相关^[27]。本研究发现PM/DM合并ILD患者血清YKL-40水平较非ILD患者显著升高,且YKL-40诊断PM/DM合并ILD的ROC曲线下面积为0.87($P<0.01$),提示YKL可作为诊断PM/DM合并ILD的生物标志物,是评估疾病严重程度标志物。相对于HRCT,血清YKL-40检测费用低廉,无放射性,更容易被患者接受,因此值得临床推广使用。以上结果提示YKL-40可用于评估PM/DM的活动度和严重程度。

本研究具有一定局限性:1)本研究为单中心研究,纳入样本受地区限制,可能对结果有一定影响;2)研究纳入样本数量较少,因此仍需要更大样本量的研究验证YKL-40在PM/DM中的诊断价值;3)本研究为横断面研究,缺乏对疾病的动态了解,因此需要队列研究证实本结论。

综上,本研究证实了血清YKL-40水平可用于评估PM/DM的活动度和严重程度,对临床具有一定指导价值。

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本文引用: 陈尚周, 周发琼. 血清YKL-40水平与多肌炎/皮肤炎的相关性[J]. *临床与病理杂志*, 2019, 39(5): 947-951. doi: 10.3978/j.issn.2095-6959.2019.05.006

Cite this article as: CHEN Shangzhou, ZHOU Faqiong. Correlation between serum YKL-40 and polymyositis/dermatomyositis[J]. *Journal of Clinical and Pathological Research*, 2019, 39(5): 947-951. doi: 10.3978/j.issn.2095-6959.2019.05.006