摘要

红细胞分布宽度与皮肌炎及多发性肌炎相关间质性肺病的关系研究

目的：

特发性炎性肌病（Idiopathic inflammatory myopathy，IIM）是一类异质性自身免疫性炎症性肌病，常见的症状包括肌肉疼痛、肌肉疲劳等。该病的主要类型包括皮肌炎（Dermatomyositis，DM）、多发性肌炎（Polymyositis，PM）、包涵体肌炎（Inclusion body myositis，IBM）、重叠性肌炎（Overlap myositis，OM）和免疫介导的坏死性肌炎（Immune-mediated necrotic myositis，IMNM)，这些病症伴随着免疫系统紊乱而发生。本研究通过收集特发性炎性肌病患者的一般资料、实验室资料及影像学检查资料，探讨红细胞分布宽度（Red blood cell distribution width，RDW）在 DM 与 PM 相关间质性肺病（interstitial lung disease，ILD）可能的病理机制，旨在进一步研究基于 RDW 预测 DM/PM 患者并发 ILD 的效能。

方法：

1. 采用回顾性横断面研究设计。收集 2018 年 6 月至 2021 年 12 月吉林大学第一医院风湿免疫科初治的 124 例 DM/PM 患者病例数据。利用 RDW 区分 DM/PM 是否合并 ILD 制作 ROC（Receiver operating characteristic curve，ROC）曲线，得到 RDW 的最佳截断值，根据 RDW 最佳截断值分为两组（升高组与正常组），比较 RDW 升高

组与正常组的组间差异；采用二元 logistic 回归分析确定与 DM/PM-ILD 相关的因素；采用 ROC 曲线评估 DM/PM-ILD 相关因素的预测价值。

2.为明确 RDW 与 DM/PM-ILD 肺功能之间的关系，本研究采用对照研究对 20 例 DM/PM-ILD 患者进行纵向随访。

结果：

（1）回顾性横断面研究共纳入 124 名患者，年龄 18-74 岁，中位年龄 52 岁（40-60 岁），男性 39 例（31.5%），女性 85 例（68.5%）。结合欧洲抗风湿病联盟/美国风湿学会（European league against rheumatism/American college of rheumatology，EULAR/ACR）于 2017 年发布的肌炎诊断及分类标准，76 名患者为 DM（61.3%），48 名患者为 PM（38.7%）；42 名合并 ILD（33.9%），其中 DM 有 27 例，PM 有 15 例，DM 组与 PM 组的 ILD 发病率无显著差异（$P > 0.05$）。亚组分析结果显示，PM 患者更容易出现乏力（$P=0.005$），皮疹（向阳疹、红斑疹、Gottron 疹）仅在 DM 患者中出现（$P < 0.001$）。PM 患者的总胆固醇（Total cholesterol，TC）水平显著高于 DM 患者（$P=0.027$），且肌酸激酶（Creatine kinase，CK）与天冬氨酸氨基转移酶（Alanine aminotransferase，ALT）水平显著高于 DM 患者（P 均 < 0.001）。所有患者均接受肌炎抗体谱检测，其中 74 例患者（59.7%）肌炎特异性抗体（Myositis specific autoantibodies，MSAs）阳性，56 例患者（45.2%）肌炎相关性抗体（Myositis associated autoantibodies，MAAs）阳性，抗 MDA5 抗体和抗 Jo-1 抗体分别检出 18 例（14.5%）。

抗 MDA5 抗体（$P < 0.001$）和抗 TIF1γ 抗体（$P=0.034$）仅在 DM 患者中检出。此外，检测出 1 例抗 Jo-1、抗 MDA5 和抗 NXP2 抗体的共存患者，1 例抗 EJ 和抗 Mi2 抗体共存患者。

（2）根据是否合并 ILD 将 DM/PM 患者分为 DM/PM-ILD 组和 DM/PM-non-ILD 组。亚组分析结果显示，发热和关节炎在 DM/PM-ILD 患者中更常见（$P=0.010$ 和 $P < 0.001$），而肌痛在 DM/PM-non-ILD 组更常见（$P=0.043$）。DM/PM-ILD 组炎症细胞浸润的频率较低（$P=0.010$）。DM/PM-ILD 组的 CK、AST、ALT、TC、LDL-C 水平均显著低于 DM/PM-non-ILD 组（P 均 < 0.05）。相反，DM/PM-ILD 组的 RDW（13.9（13.0-15.8） vs. 13.3（12.7-14.1），$P=0.012$）和 IgM 水平（$P=0.039$）显著高于 DM/PM-non-ILD 组。与 DM/PM-non-ILD 组相比，DM/PM-ILD 组肌炎抗体如抗 MDA5 抗体、抗 Jo-1 抗体和抗 Ro52 抗体检出率显著更高（P 均 < 0.001）。

（3）RDW 亚组分析显示，RDW 正常组临床表现中肌痛更为常见（$P=0.012$），而 RDW 升高组 ILD 更为常见（$P=0.009$）。RDW 升高组超敏 C 反应蛋白（Hypersensitive C-reactive protein，hsCRP）水平显著高于 RDW 正常组（$P=0.027$）。相较于 RDW 正常组，RDW 升高组补体 4（Complement 4，C4）水平更低（$P=0.036$）。

（4）应用单因素及多因素二元 logistic 回归分析发现，除了抗 MDA5 和抗 Jo-1 抗体等公认的独立危险因素外，RDW 值升高是 DM/PM-ILD 的独立危险因素（OR=1.635，95%CI 1.172-2.281，$P=0.004$，RDW 为连续数值型变量；OR=3.145，95%CI 1.079-9.168，$P=0.036$，

RDW 为二分类变量）。

（5）RDW（二分类变量）联合抗 MDA5 抗体绘制 DM/PM-ILD 的 ROC 曲线，显示此模型的 AUC 为 0.723（95%CI 0.626-0.820），敏感度 73.8%, 特异性为 64.6%，阳性预测值为 72.2%，阴性预测值为 72.6%；RDW（二分类变量）联合抗 Jo-1 抗体绘制 DM/PM-ILD 的 ROC 曲线，显示此模型的 AUC 为 0.731（95%CI 0.634-0.829），敏感度 73.8%, 特异性为 63.4%，阳性预测值为 77.8%，阴性预测值为 73.6%。

RDW（连续数值型变量）联合抗 MDA5 抗体绘制 DM/PM-ILD 的 ROC 曲线，显示此模型的 AUC 为 0.743（95%CI 0.646-0.839），敏感度 54.8%, 特异性为 87.8%，阳性预测值为 69.2%，阴性预测值为 75.5%；RDW（连续数值型变量）联合抗 Jo-1 抗体绘制 DM/PM-ILD 的 ROC 曲线，显示此模型的 AUC 为 0.736（95%CI 0.633-0.840），敏感度 54.8%, 特异性为 90.2%，阳性预测值为 74.1%，阴性预测值为 78.9%。

（6）对照研究共纳入 20 例 DM/PM-ILD 患者，结果显示：基线时 20 例患者的肺弥散功能均有一定的损害（表现为 DLCO < 80%），给予治疗后随访第 3 个月时，随着肺弥散功能的改善，RDW 值也随之降低（P=0.016）。20 例患者中随访第 3 个月时有 3 例患者肺功能损害进一步加重，其中 2 例患者的 RDW 值也进一步升高，1 例患者 RDW 值无明显变化。

结论：

（1）RDW 联合抗 MDA5 抗体或抗 Jo-1 抗体是 DM/PM-ILD 的

显著预测指标。

（2）RDW 与 DM/PM-ILD 相关，DM/PM-ILD 患者相较于无 ILD 患者 RDW 值更高，且随肺功能变化。

关键词：

红细胞分布宽度，皮肌炎，多发性肌炎，间质性肺病

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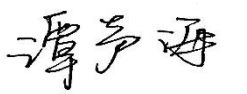
作者签名：  指导教师签名： 

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Abstract

Study of the relationship between red blood cell distribution width in dermatomyositis and polymyositis-related interstitial lung disease

Objective:

Idiopathic inflammatory myopathy (IIM) is a heterogeneous group of autoimmune inflammatory myopathies with common symptoms including muscle pain and muscle fatigue. The main types of the disease include dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), overlap myositis (OM) and immune-mediated necrotic myositis (IMNM), which occur in association with immune system disorders. In this study, we investigated the possible pathological mechanisms of red blood cell distribution width (RDW) in DM and PM-related interstitial lung disease (ILD) by collecting general data, laboratory data and imaging data from patients with idiopathic inflammatory myopathies. The aim was to further investigate the efficacy of RDW-based prediction of concomitant ILD in DM/PM patients.

Methods:

1. A retrospective cross-sectional study design was used. Data were

collected on 124 cases of DM/PM patients initially treated in the Department of Rheumatology and Immunology, First Hospital of Jilin University from June 2018 to December 2021. Receiver operating characteristic curves were made using RDW to distinguish whether DM/PM was combined with ILD to obtain the optimal cut-off value of RDW, and the two groups (elevated and normal groups) were divided into two groups according to the optimal cut-off value of RDW to compare the group differences between the elevated and normal groups of RDW; binary logistic regression analysis was used to determine the factors associated with DM/PM-ILD; the ROC curve was used to assess the predictive value of the factors associated with DM/PM-ILD.

2. To clarify the relationship between RDW and lung function in DM/PM-ILD, this study used a controlled study of 20 patients with DM/PM-ILD with longitudinal follow-up.

Results:

(1) A total of 124 patients were included in the retrospective cross-sectional study, aged 18-74 years, with a median age of 52 years (40-60 years), 39 males (31.5%), and 85 females (68.5%). According to the diagnostic and classification criteria for myositis released by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) in 2017, 76 patients were diagnosed with DM (61.3%) and

48 patients with PM (38.7%). 42 patients had ILD (33.9%), including 27 in the DM group and 15 in the PM group, and there was no significant difference in the ILD incidence rate between the DM group and the PM group ($P > 0.05$). Subgroup analysis results showed that PM patients are more likely to experience fatigue ($P = 0.005$), and the rashes (heliotrope, erythematous patches, Gottron rash) only appeared in DM patients ($P < 0.001$). The total cholesterol (TC) level of PM patients was significantly higher than that of DM patients ($P = 0.027$), and the creatine kinase (CK) and alanine aminotransferase (ALT) levels were significantly higher than those of DM patients ($P < 0.001$). All patients underwent myositis antibody spectroscopy, of which 74 (59.7%) had positive myositis specific autoantibodies (MSAs), and 56 (45.2%) had positive myositis associated autoantibodies (MAAs), and 18 (14.5%) were positive for anti-MDA5 antibodies and anti-Jo-1 antibodies, respectively. Anti-MDA5 antibodies ($P < 0.001$) and anti-TIF1γ antibodies ($P = 0.034$) were only detected in DM patients. In addition, one patient was detected with coexistence of anti-Jo-1, anti-MDA5 and anti-NXP2 antibodies, and one patient was detected with coexistence of anti-EJ and anti-Mi2 antibodies.

(2) Patients with DM/PM were divided into DM/PM-ILD and DM/PM-non-ILD groups according to whether there was complicated ILD. Subgroup analysis showed that fever and arthritis were more common in the DM/PM-ILD patients ($P = 0.010$, $P < 0.001$), while myalgia was more

common in the DM/PM-non-ILD group (P = 0.043). The frequency of inflammatory cell infiltration was lower in the DM/PM-ILD group (P = 0.010). The levels of CK, AST, ALT, TC and LDL-C in the DM/PM-ILD group were significantly lower than those in the non-ILD group ($P < 0.05$); on the contrary, the RDW (13.9 (13.0-15.8) vs. 13.3 (12.7-14.1), $P = 0.012$) and IgM levels (P = 0.039) in the DM/PM-ILD group were significantly higher than those in the DM/PM-non-ILD group. Compared with the DM/PM-non-ILD group, the detection rate of myositis antibodies such as anti-MDA5 antibodies, anti-Jo-1 antibodies and anti-Ro52 antibodies were significantly higher in the DM/PM-ILD group ($P < 0.001$).

(3) Subgroup analysis of RDW showed that myalgia was more common in the RDW normal group (P = 0.012), while ILD was more common in the RDW high group (P = 0.009). In the RDW high group, hypersensitive C-reactive protein (hsCRP) was significantly higher than the RDW normal group (P = 0.027). Compared with the RDW normal group, the level of complement 4 (C4) was lower in the RDW high group ($P = 0.036$).

(4) Univariate and multivariate binary logistic regression analysis found that in addition to anti-MDA5 and anti-Jo-1 antibodies and other recognized independent risk factors, Elevated RDW values are an independent risk factor for DM/PM-ILD (OR = 1.635, 95%CI 1.172-2.281, P = 0.004, RDW as a continuous numerical variable; OR = 3.145, 95%CI

1.079-9.168, $P = 0.036$, RDW as a dichotomous variable).

(5) RDW (dichotomous variable) combined with anti-MDA5 antibody plotted the ROC curve for DM/PM-ILD, showing an AUC of 0.723 (95% CI 0.626-0.820), sensitivity of 73.8%, specificity of 64.6%, positive predictive value of 72.2%, and negative predictive value of 72.6% for this model; RDW (dichotomous variable) combined with anti-Jo- 1 antibody in combination with anti-Jo-ILD showed an AUC of 0.731 (95% CI 0.634-0.829), sensitivity of 73.8%, specificity of 63.4%, positive predictive value of 77.8% and negative predictive value of 73.6%.

ROC curves for DM/PM-ILD with RDW (continuous numerical variables) in combination with anti-MDA5 antibody showed an AUC of 0.743 (95% CI 0.646-0.839), sensitivity of 54.8%, specificity of 87.8%, positive predictive value of 69.2% and negative predictive value of 75.5%; RDW (continuous numerical variables) in combination with anti-Jo-1 antibody showed an AUC of 0.736 (95% CI 0.633-0.840), sensitivity of 54.8%, specificity of 90.2%, positive predictive value of 74.1% and negative predictive value of 78.9%.

(6) A total of 20 cases of DM/PM-ILD were included in the study results: all 20 patients had some impairment in diffusing lung function (manifested as DLCO < 80%) at baseline, and after administration of the treatment, RDW values decreased as diffusing lung function improved at the third month of follow-up ($P = 0.016$). Among the 20 patients, three

patients had further aggravation of pulmonary impairment at the third month of follow-up, including two patients who also had a further increase in RDW value and one patient who had no significant change in RDW value.

Conclusion:

(1) RDW combined with anti-MDA5 antibody or anti-Jo-1 antibody was a significant predictor of DM/PM-ILD.

(2) RDW was associated with DM/PM-ILD and patients with DM/PM-ILD had higher RDW values compared to patients without ILD, which varied with lung function.

Key words:

Red cell distribution width, Dermatomyositis, Polymyositis, Interstitial lung disease