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INTERSTITIAL LUNG DISEASE

Utility of Coagulation Markers for the Prediction of Rapidly Progressive Interstitial Lung Disease in Patients with Dermatomyositis

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Abstract

We aimed to evaluate the utility of coagulation markers for the prediction of rapidly progressive interstitial lung disease (RP-ILD) in patients with dermatomyositis (DM). In this retrospective study, 29 patients with DM-associated ILD were analyzed. The number of patients with RP-ILD was 15 (52%). The baseline clinical and demographic data and laboratory markers were analyzed to identify predictive factors for RP-ILD.The univariate logistic regression analysis demonstrated that in addition to well-known laboratory markers, such as serum ferritin, KL-6, and lymphocyte counts, a prolonged activated partial thromboplastin time (aPTT) ratio at the time of DM-associated ILD diagnosis was useful for predicting RP-ILD. Moreover, the logistic regression model and receiver operating characteristic curve analysis showed that combinations of the aPTT ratio and well-known laboratory markers were significantly effective in predicting RP-ILD. This study suggested that an association between RP-ILD and the coagulation system exists.

Keywords Dermatomyositis · Interstitial lung disease · Rapidly progressive interstitial lung disease · Activated partial thromboplastin time

Introduction

Dermatomyositis (DM) is frequently complicated by interstitial lung disease (ILD), and some patients with DM have rapidly progressive interstitial lung disease (RP-ILD) resulting in fatal respiratory failure [1, 2].

Prediction of RP-ILD might prompt a decision to initiate a more aggressive therapy and follow the patient more closely. Therefore, factors predictive of RP-ILD are important in the management of patients with DM. Previous studies focused on several laboratory markers including myositis-specific autoantibodies, serum ferritin levels, and blood lymphocyte counts [3, 4]; however, these markers alone seem to be insufficient to predict of all RP-ILD cases.

Recently, the coagulation cascade has been reported to be important in the acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) [5]. Indeed, the levels of several markers of coagulation and fibrinolysis were reported to be elevated in a case of AE of IPF [6, 7]. However, the association between the coagulation system and DM-associated RP-ILD remains unclear.

In this study, we evaluated the utility of coagulation markers for the prediction of RP-ILD in a cohort of patients with DM.

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Methods

Patients

This was a single-center, retrospective cohort study conducted at Kyoto Prefectural University of Medicine in Japan, wherein 59 consecutive patients with DM-associated ILD, admitted from January 2008 to September 2017, were investigated.

To eliminate the influence of drugs, other connective tissue diseases, and malignant tumors on the coagulation markers, the following patients were excluded: patients who had undergone immunosuppressive therapy before admission to our institution ($n=25$); those with other concomitant connective tissue diseases ($n = 3$); those with a concomitant malignant tumor ($n=1$), and those currently undergoing anticoagulation treatment ($n=1$). After application of the exclusion criteria, 29 patients were included in the analysis. At the time of DM-associated ILD diagnosis, no patient exhibited respiratory failure, and had a history of a thromboembolic event, hemorrhagic event, pulmonary infarction, cirrhosis, recent infection, cerebrovascular accident, heart failure, or acute coronary syndrome.

The baseline clinical and demographic data and laboratory findings including coagulation markers were obtained from the patients' medical records on admission.

Diagnosis

All investigated patients exhibited skin rash, myopathy, respiratory symptoms, or a combination thereof at admission, and were diagnosed with DM or clinically amyopathic dermatomyositis (CADM) [8, 9].

According to the diagnostic criteria for AE of IPF [10], RP-ILD was defined as follows in this study: presentation of respiratory failure requiring oxygen therapy within 1 month after the DM-associated ILD diagnosis, accompanied by bilateral new ground-glass opacity (GGO) or consolidation, which could not be fully explained by cardiac failure, fluid overload, or infection.

Data Collection

The laboratory test items evaluated were creatine kinase; lactate dehydrogenase; alanine aminotransferase; aspartate aminotransferase; Krebs von den Lungen-6 (KL-6); C-reactive protein; ferritin; prothrombin time (PT) ratio and activated partial thromboplastin time (aPTT) ratio between patients and normal controls; white blood cell, lymphocyte, and platelet counts; hemoglobin; anti-aminoacyl-transfer RNA synthetase antibodies (anti-ARS Ab); and anti-melanoma differentiation-associated gene 5 antibodies (anti-MDA5 Ab). Anti-ARS Ab and anti-MDA5 Ab were determined as described previously [11].

Thromborel S (Sysmex Corporation, Kobe, Japan) and aPTT-SLA (Sysmex Corporation) were used as PT and aPTT reagents, respectively. Normal plasma samples (Coagtrol N, LSI Medience Corporation, Tokyo, Japan) were used to calculate PT and aPTT ratios.

D-dimer level measurement and pulmonary function test results were not analyzed owing to a lack of data.

High-Resolution Computed Tomography (HRCT) Evaluation

We obtained HRCT of the chest, and the images were reviewed by three independent observers (T.K., T.I., and T.S.) blinded to the respective clinical information. Interobserver disagreements were resolved by consensus. The images were assessed for the presence of GGO, consolidation, and reticulation (Supplementary Fig. 1a–c). We designated the most extensive of each finding as the dominant findings. The predominant distribution of abnormalities on HRCT findings was evaluated as previously reported [12].

Statistical Analyses

Categorical variables are presented as the frequency and percentage. Continuous variables are expressed as the median value (interquartile range), unless stated otherwise. We adopted logistic regression models to identify factors predictive of RP-ILD. Variables in logistic regression models were selected based on previous reports and clinical significance. Results of the regression models are shown as the odds ratio (OR) and 95% confidence interval (CI). The coagulation markers, significant in the univariate analysis, were included in the analysis to adjust for other significant variables in the univariate analysis. Each pair of variables was displayed in a scatter plot, as needed. To evaluate the discriminatory ability of each parameter, the area under the receiver operating characteristic (ROC) curve (AUC) was measured. For statistical tests, the level of significance was set at 5%. All statistical analyses were performed with EZR (version 1.36) (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The study was approved by the ethics committee of Kyoto Prefectural University of Medicine and the study complied with the Declaration of Helsinki guidelines. Because of the anonymous nature of the data, the requirement for informed consent was waived.

Results

Patient Characteristics

The clinical characteristics and laboratory data of the all the patients are shown in Table 1. No patient had RP-ILD at diagnosis, and subsequently, 15 (52%) of the patients developed RP-ILD. Anti-ARS Ab and anti-MDA5 Ab, except anti-Jo-1 Ab, were not measured in 9 patients, because the commercial reagents for measuring anti-ARS Ab and anti-MDA5 Ab were unavailable until 2014 and 2016, respectively. Among the 20 patients whose anti-ARS Ab and anti-MDA5 Ab levels were measured, nine were anti-ARS Ab+, seven were anti-MDA5 Ab+, and four were anti-ARS Ab−/anti-MDA5 Ab−. No patient had anti-ARS Ab and anti-MDA5 Ab together.

The dominant HRCT findings of the patients at the time of diagnosis are shown in Supplementary Table 1. Consolidation was most frequent especially in patients with RP-ILD, and abnormal findings were predominant, craniocaudally in the lower or random/diffuse region, and axially in the peripheral region.

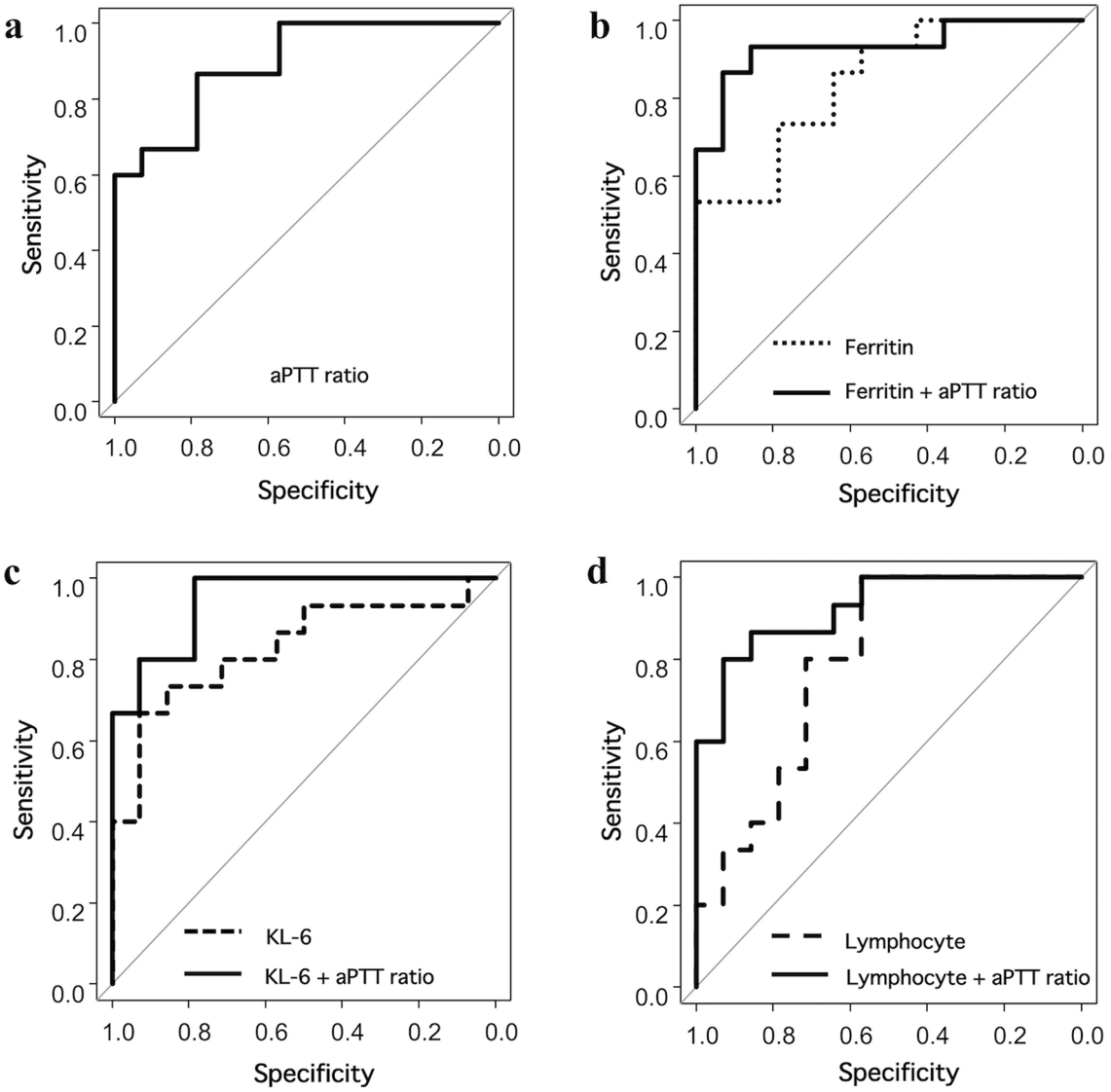

Fig. 1 A receiver operating characteristic (ROC) curve to predict rapidly progressive interstitial lung disease (RP-ILD). The area under the ROC curve (AUC) of each parameter for the prediction of RP-ILD is shown with the 95% confidence interval (CI). **a** *aPTT ratio* activated partial thromboplastin time ratio between patients and normal controls: AUC 0.895; 95% CI 0.784–1.00. **b** Ferritin: AUC 0.843; 95% CI 0.702–0.984, Ferritin + aPTT ratio: AUC 0.933; 95% CI 0.838–1.00. **c** *KL-6* Krebs von den Lungen-6: AUC 0.829; 95% CI 0.671–0.986, KL-6 + aPTT ratio: AUC 0.948; 95% CI 0.876–1.00. **d** Lymphocyte: AUC 0.790; 95% CI 0.617–0.964. Lymphocyte + aPTT ratio: AUC 0.924; 95% CI 0.832–1.00. [a] activated partial thromboplastin time ratio between patients and normal controls; [b] Krebs von den Lungen-6

Table 1 Clinical characteristics of all enrolled patients ($n=29$)

Characteristic	Without RP-ILD ($n=14$)	RP-ILD ($n=15$)	Total ($n=29$)
Age (years)	57.5 (49–63)	60 (51.5–73)	60 (49–66)
Male sex, *n* (%)	5 (36)	8 (53)	13 (45)
CADM, *n* (%)	6 (43)	10 (67)	16 (55)
Anti-ARS Ab and anti-MDA5 Ab			
Measured, *n*	11	9	20
Anti-ARS Ab+, *n* (%)	6 (55)	3 (33)	9 (45)
Anti-MDA5 Ab+, *n* (%)	2 (18)	5 (56)	7 (35)
Double-negative, *n* (%)	3 (27)	1 (11)	4 (20)
Unmeasured (except anti-Jo-1 Ab), *n*	3	6	9
Laboratory data			
PT ratio	1.01 (0.95–1.02)	1.01 (0.96–1.06)	1.01 (0.95–1.03)
aPTT ratio	1.08 (1.06–1.21)	1.42 (1.24–1.65)	1.23 (1.09–1.42)
LDH (U/L)	341 (318–520)	627 (326–794)	426 (319–683)
KL-6 (U/mL)	548 (480–883)	1014 (871–1477)	906 (537–1034)
CRP (mg/dL)	0.43 (0.15–1.4)	1.1 (0.87–2.6)	0.87 (0.44–1.9)
Ferritin (ng/mL)	156 (73–438)	830 (446–3673)	449 (144–830)
AST (U/L)	55 (46–92)	104 (72–418)	78 (50–128)
ALT (U/L)	48 (26–59)	79 (39–198)	54 (30–119)
CK (U/L)	381.5 (222–3596)	391 (162–1297)	391 (166–1698)
WBC counts (/μL)	7750 (6325–9500)	5800 (4450–6650)	6400 (4700–8400)
Lymphocyte counts (/μL)	1615 (865–2125)	780 (555–890)	890 (710–1610)
Hb (g/dL)	12.3 (11.7–13.4)	12.2 (11.5–14.1)	12.3 (11.5–13.6)
Plt counts (10^4/μL)	24.8 (19.7–30.9)	17.1 (12.0–28.2)	23.1 (14.3–29.1)

Continuous variables are expressed as the median value (interquartile range)

RP-ILD Rapidly progressive interstitial lung disease, *CADM* Clinically amyopathic dermatomyositis, *anti-ARS Ab* + anti-aminoacyl-transfer RNA synthetase antibody, *anti-MDA5 Ab* + antimelanoma differentiation-associated gene 5 antibody, *PT* prothrombin time ratio between patients and normal controls, *aPTT* activated partial thromboplastin time ratio between patients and normal controls, *LDH* lactatae dehydrogenase, *KL-6* Krebs von den Lungen-6, *CRP* C-reactive protein, *AST* aspartate transaminase, *ALT* alanine transaminase, *CK* creatine kinase, *WBC* white blood cells, *Hb* hemoglobin, *Plt* platelet

HRCT findings, when the patients developed RP-ILD, consisted of bilateral new ground-glass opacity (GGO) or consolidation, representing diffuse alveolar damage (DAD).

Almost all patients underwent combination therapies including prednisolone, methylprednisolone pulse therapy, intravenous cyclophosphamide pulse therapy, treatment with a calcineurin inhibitor, and plasma exchange. The treatment was not codified and was at the discretion of each treating clinician (Supplementary Table 2).

Mortality within 90 days after DM-associated ILD diagnosis occurred only in patients with RP-ILD ($n=5$).

None of the patients without RP-ILD showed respiratory failure within 90 days.

Factors Predictive of RP-ILD

The univariate logistic regression analysis revealed that increased serum ferritin level, KL-6 level, and aPTT ratio; and decreased lymphocyte counts were significantly associated with RP-ILD (Table 2).

After adjusting for serum ferritin level, serum KL-6 level, and blood lymphocyte counts, adjusted OR of aPTT ratio for 0.1 increase was 2.80 (95% CI 1.03–7.60; $P=0.044$), 3.90 (95% CI 0.968–15.7; $P=0.057$), and 2.41(95% CI 1.01–5.74; $P=0.047$), respectively.

The AUC value of the combination of the aPTT ratio and serum ferritin, serum KL-6, and blood lymphocyte counts was 0.933 (95% CI 0.838–1.00), 0.948 (95% CI 0.876–1.00), and 0.924 (95% CI 0.832–1.00), respectively. For combinations of aPTT ratio and these variables, the AUC values were higher than those of each parameter alone (Fig. 1).

Some patients with RP-ILD exhibited an increased aPTT ratio, whereas, serum ferritin or KL-6 values were not elevated at baseline (Supplementary Fig. 2).

Table 2 Factors predictive of rapidly progressive interstitial lung disease in patients with dermatomyositis

Variables	Univariate logistic regression analysis		
	OR	95% CI	*P*
CADM	2.67	0.590–12.0	0.20
PT ratio, each 0.1 increase	1.63	0.578–4.61	0.36
aPTT ratio, each 0.1 increase	2.99	1.24–7.20	0.014
CRP, mg/dL	1.87	0.776–4.53	0.16
KL-6, each 100 U/mL increase	1.50	1.08–2.09	0.017
Ferritin, each 100 ng/mL increase	1.44	1.03–2.00	0.032
LDH, each 100 U/L increase	1.35	0.954–1.92	0.09
AST, U/L	1.01	0.997–1.02	0.14
CK, U/L	1.00	0.999–1.00	0.38
WBC counts, each 100/μL decrease	1.02	0.990–1.04	0.17
Lymphocyte counts, each 100/μL decrease	1.31	1.04–1.64	0.021
Plt counts, each 10,000/μL decrease	1.06	0.980–1.14	0.13

Except where indicated otherwise, odds ratio was calculated for each 1-unit increase

OR odds ratio, *95% CI* confidence interval, *CADM* clinically amyopathic dermatomyositis, *PT* prothrombin time ratio between patients and normal controls, *aPTT* activated partial thromboplastin time ratio between patients and normal control, *CRP* C-reactive protein, *KL-6* Krebs von den Lungen-6, *LDH* lactatae dehydrogenase, *AST* aspartate transaminase, *CK* creatine kinase, *WBC* white blood cells, *Plt* platelet

Discussion

In this study, we have demonstrated that the aPTT ratio at the time of DM-associated ILD diagnosis was useful for predicting RP-ILD, and that the combination of the aPTT ratio and well-known markers was more effective for the prediction of RP-ILD. In particular, the aPTT ratio might be useful even if the serum ferritin or KL-6 level is not elevated. To our knowledge, this is the first study to report the utility of aPTT in patients with DM-associated ILD.

An AE of IPF demonstrates a histological pattern of DAD corresponding with acute respiratory distress syndrome [13]; extravascular and intra-alveolar thrombin activation following epithelial and endothelial injury are pathological hallmarks of DAD [14]. In addition, the role of endothelial injury in the development of DM-associated ILD has been postulated [15]. Thus, we speculated that RP-ILD might also be associated with the coagulation system, and consequently lead to the aPTT prolongation observed in patients with RP-ILD.

This study has some limitations. First, it was a small, single-center, retrospective study. The possibility of unintentional selection bias could not be fully excluded. In addition, all four variables could not be included in the multivariate analysis model because the number of cases was insufficient. Second, the measurement of aPTT has not been standardized, and the results vary according to several factors such as the instrumentation and reagent used. Accordingly, our findings need to be validated in a future prospective study across different facilities. Third, the cause of aPTT prolongation could not be systematically investigated due to a lack of data. Antiphospholipid antibody syndrome is accompanied by aPTT prolongation without any deficiency of respective coagulation factor and is associated with endothelial dysfunction [16, 17]. Therefore, it may be worth investigating the association between RP-ILD and antiphospholipid antibody in a future study.

In conclusion, we demonstrated that aPTT prolongation in addition to the serum ferritin level, KL-6 level, and lymphocyte counts could be useful for the prediction of RP-ILD in a cohort of patients with DM. This result may aid in the early identification of patients with DM who have an increased risk for developing RP-ILD and may contribute to improving the survival rate of these patients.

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Compliance with Ethical Standards

Conflict of interest The authors declared that they have no conflict of interest.

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