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ORIGINAL RESEARCH

Clinical Significance and Correlation of Plasma D-Dimer, Fibrinogen, and Cytokines in Idiopathic Inflammatory Myopathy

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Purpose: To investigate the clinical significance and correlation of plasma D-dimer, fibrinogen (FIB), and serum cytokines in patients with idiopathic inflammatory myopathy (IIM).

Patients and Methods: Fifty patients with IIM and 50 healthy controls were included. Plasma D-dimer, FIB, and serum cytokine levels in IIM patients were analyzed and contrasted with the control group. The association between coagulation indicators and key clinical indices, as well as cytokines was also analyzed in IIM patients. Subgroup analyses were performed based on the presence of interstitial lung disease (ILD). Correlations among the variables were tested using Spearman correlation analysis.

Results: The levels of D-dimer, FIB, interleukin (IL)-1β, IL-6, IL-8, IL-18, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were significantly higher in the IIM group compared to healthy controls (all $p \leq 0.001$). In IIM patients, plasma D-dimer was positively correlated with serum alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and ferritin, while negatively correlated with manual muscle test (MMT8) score, peripheral blood lymphocyte count, and hemoglobin ($p < 0.05$). Plasma FIB was positively associated with C-reactive protein, ESR, and ferritin ($p < 0.05$). Additionally, plasma D-dimer showed significantly positive correlations with IL-1β ($r = 0.325$, $p = 0.021$), IL-6 ($r = 0.309$, $p = 0.029$), IL-8 ($r = 0.347$, $p = 0.014$), and IL-18 ($r = 0.333$, $p = 0.018$). In subgroup analyses, serum IFN-γ levels were significantly higher in IIM patients with ILD compared to those without ILD ($p = 0.021$), while no significant differences were observed in D-dimer or FIB levels between these two groups.

Conclusion: Elevated plasma D-dimer in IIM patients may be associated with disease activity, with cytokines playing a potentially important role. Both D-dimer and cytokines hold clinical significance in evaluating the disease status of IIM patients.

Keywords: D-dimer, Fibrinogen, idiopathic inflammatory myopathy, inflammation, disease activity, interstitial lung disease

Introduction

Idiopathic inflammatory myopathy (IIM) comprises a heterogeneous group of autoimmune inflammatory diseases that primarily affect the skin, muscles, lungs, heart, and other organs. Adult IIM is subclassified into dermatomyositis (DM), antisynthetase syndrome (ASS), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM),[1] with DM and ASS being the most prevalent conditions.[2,3] Among patients with IIM, interstitial lung disease (ILD) occurs in 20% to 78% of cases, representing a major cause of morbidity and mortality in this clinical group.[4]

Although the precise pathogenesis of IIMs remains unclear, evidence suggests that various immune cells such as T cells, B cells, dendritic cells, and macrophages, as well as their secreted cytokines and chemokines, contribute to the development of the disease.[5] Cytokines such as interleukin (IL)-1β, IL-18, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ are highly expressed in the muscle tissues of IIM patients.[6] Other studies have shown that IL-6, IL-8, and TNF-α correlate with disease activity, particularly in cases complicated by ILD.[7] Moreover, a growing body of evidence has

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revealed an extensive cross-talk between inflammatory and coagulation pathways, wherein inflammation activates coagulation, while coagulation, in turn, exacerbates inflammation.[8]

D-dimer is a soluble fibrin degradation product, which is generated through the fibrinolytic breakdown of thrombi.[9] Fibrinogen (FIB), a key regulator of thrombin, binds to external site II of thrombin, thereby increasing its activity and promoting the formation of fibrin clots.[10] Both D-dimer and FIB serve as markers of coagulation and fibrinolysis activation and are thus commonly used in the clinical evaluation of venous thromboembolism (VTE). Notably, D-dimer and FIB levels increase rapidly in inflammatory conditions. Immune and coagulation systems are functionally interconnected,[11] and chronic inflammation has been implicated in disturbances of normal coagulation in several autoimmune conditions.[12]

Previous studies have demonstrated that plasma D-dimer and FIB levels are significantly elevated in various rheumatic disorders and are positively correlated with disease activity, including in conditions such as rheumatoid arthritis and ANCA-associated vasculitis.[13,14] However, their predictive value in patients with IIM remains poorly understood. To address this, this study examined the clinical significance and correlation of plasma D-dimer, FIB, and serum cytokines in patients with IIM to assess whether coagulation-related serves as potential indicators of disease activity.

Materials and Methods

Study Population

This was a single-center, cross-sectional study comprising 50 patients diagnosed with IIM between July 2022 and December 2023 at Jining No.1 People's Hospital. All participants met the 2017 European League Against Rheumatism/ American College of Rheumatology Classification Criteria for Adult Idiopathic Inflammatory Myopathies and had active or uncontrolled disease.[15] Patients were excluded if they had active infection, malignant tumors, other autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus, had received anticoagulation therapy or chemotherapy prior to enrolment, had undergone major surgery or experienced trauma within the preceding three months, had a known coagulation disorder; or were pregnant. Patients with IIM were further stratified into two subgroups based on the presence or absence of ILD. A diagnosis of ILD was determined according to the patient's clinical presentation and high-resolution computed tomography (HRCT) findings, including ground-glass opacities, honeycombing, and/or fibrosis. An additional group of 50 age- (± 3 years) and sex- matched control individuals (HCs) was recruited from the Center of Physical Examination at Jining No.1 People's Hospital. The study protocol was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the Jining No.1 People's Hospital, with all participants providing written informed consent.

Clinical and Laboratory Assessments

Participant demographic and clinical characteristics, including gender, age, disease duration, body mass index (BMI), diagnosis, symptoms, signs, and the presence of thromboembolic disease, were extracted from electronic medical records. Clinical manifestations assessed included characteristic skin findings such as heliotrope rash, mechanic's hands, Gottron's papules, shawl sign, V-neck sign, and skin ulcers, as well as symptoms of myalgia, muscular weakness, arthralgia, and Raynaud's phenomenon. Muscle strength was measured using the manual muscle test (MMT8) proposed by the International Myositis Outcome Assessment Collaborative Study. Myositis-specific antibodies (MSAs) including anti-MDA-5, NXP2, Mi-2, TIF1-γ, SAE, Jo-1, PL-12, PL-7, EJ, OJ, and SRP, along with myositis-associated autoantibodies (MAAs), including Ku, Ro52, and PM-Scl75/100, were analyzed. Serum MSAs and MAAs were detected via immunoblotting according to the manufacturer's instructions (Simcere Medical Laboratory Co., Ltd., Nanjing, Jiangsu, China).

Venous blood samples were obtained from all participants following an overnight fast. Plasma D-dimer and FIB levels were measured using an automated coagulation analyzer. The normal reference range of D-dimer was below 0.5 mg/L, and for FIB below 4.98g/L. Blood samples were centrifuged immediately to extract serum, which was then stored at −80 degree centigrade for subsequent cytokine quantification. Routine laboratory blood parameters were also

measured, including alanine aminotransferase (ALT), aspartate transaminase (AST), creatine kinase (CK), lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, immunoglobulin, and complement factors were measured. All laboratory analyses were conducted by the Central Laboratory Department of the study hospital. HRCT was performed in all IIM patients to evaluate lung abnormalities associated with ILD. In IIM patients with elevated D-dimer or FIB, lower extremity venous ultrasonography was performed within 24 hours of obtaining coagulation results to assess for deep vein thrombosis.

Serum levels of IL-1β, IL-6, IL-8, IL-18, TNF-α, and IFN-γ were quantified using enzyme-linked immunosorbent assays (ELISA) (Jiangsu Meimian Industrial Co.,Ltd., Yancheng, Jiangsu, China), following the manufacturer's protocol.

Statistical Analysis

Continuous variables are reported using means and standard deviations for normally distributed data and medians with interquartile ranges (IQR) for non-normally distributed data. Group comparisons were made using The Student's *t*-test or Mann–Whitney *U*-test. Multiple comparisons of quantitative data were calculated using the Kruskal–Wallis *H*-test (non-normal distribution) followed by Dunnett's test. Categorical variables are reported as frequencies and percentages and were analyzed using the chi-square test. Correlations between variables were tested using Spearman rank correlation analysis. Statistical significance was set at $p < 0.05$, with all reported p values being two-sided. Statistical analyses were performed using GraphPad Prism 9.0 software.

Results

Baseline Characteristics of the Study Population

A total of 50 patients with IIM were included in the study, comprising 21 with DM (including 1 case of amyopathic dermatomyositis, ADM), 6 with PM, 21 with ASS, and 2 with IMNM. The demographic and clinical characteristics of the IIM patients are summarized in Table 1. The mean age of IIM patients was 56.00±11.99 years, with females

Table 1 Comparison of Clinical Characteristics and Laboratory Examinations Between IIM Patients with and without ILD

Variables	All (n = 50)	IIM with ILD (n = 35)	IIM without ILD (n = 15)	p (ILD vs non-ILD)
Demographics				
Age, years	56.00±11.99	54.83±11.18	58.73±13.72	0.296
Female, n (%)	39 (78.0)	27 (77.1)	12 (80.0)	0.882
PM, DM, ASS, IMNM, n	6, 21, 21, 2	4, 9, 21, 1	2, 12, 0, 1	
Duration, months	24 (5.5–48)	24 (6–48)	36 (1–120)	0.781
BMI (kg/m^2)	23.66±3.26	24.24±3.56	22.30±1.89	0.053
Complications, n (%)				
Hypertension	14 (28.0)	9 (25.7)	5 (33.3)	
Diabetes	8 (16.0)	4 (11.4)	4 (26.7)	
Coronary heart disease	5 (10.0)	3 (8.6)	2 (13.3)	
Cerebrovascular disease	6 (12.0)	3 (8.6)	3 (20.0)	
Clinical manifestations, n (%)				
Rash	34 (68.0)	22 (62.9)	12 (80.0)	0.390
Myalgia	17 (34.0)	11 (31.4)	6 (40.0)	0.794
Muscular weakness	21 (42.0)	13 (37.1)	9 (60.0)	0.238
Arthralgia	16 (32.0)	13 (37.1)	3 (20.0)	0.390
Raynaud's phenomenon	6 (12.0)	6 (17.1)	0 (0.0)	0.217
MMT8 score	76.00 (71.00–80.00)	78.00 (72.00–80.00)	73.00 (62.00–77.00)	0.011*

(*Continued*)

Table 1 (Continued).

Variables	All (n = 50)	IIM with ILD (n = 35)	IIM without ILD (n = 15)	p (ILD vs non-ILD)
Laboratory examination				
WBC (×10^9/L)	8.17 (5.28–10.98)	8.66 (5.38–11.00)	6.78 (4.99–10.97)	0.512
LYM (×10^9/L)	1.50±0.56	1.52±0.59	1.45±0.51	0.660
Hb (g/L)	122.90±15.40	123.10±15.43	122.50±15.85	0.893
PLT (×10^9/L)	243.30±96.30	245.50±83.85	238.30±123.90	0.813
ALT (U/L)	25.15 (16.90–60.60)	24.30 (16.00–45.30)	30.70 (18.90–99.10)	0.326
AST (U/L)	27.00 (19.00–78.25)	24.00 (19.00–49.80)	36.00 (15.90–188.00)	0.369
CK (U/L)	84.85 (45.60–538.10)	73.80 (46.80–342.30)	284.00 (42.00–2319.00)	0.163
LDH (U/L)	321.00 (247.60–499.80)	294.50 (243.00–380.00)	444.90 (291.40–768.00)	0.028*
CRP (mg/dl)	6.63 (3.41–19.23)	8.73(3.43–22.30)	4.01 (3.41–12.90)	0.185
ESR (mm/h)	24.50 (14.75–46.75)	21.00 (15.00–44.00)	38.00 (12.00–51.00)	0.634
Ferritin (ng/mL)	188.70 (46.75–491.80)	114.40 (46.00–448.20)	265.60 (62.85–719.50)	0.378
IgA (mg/dl)	2.95±1.24	2.89±1.11	3.09±1.51	0.611
IgM (mg/dl)	1.25 (0.89–1.79)	1.31 (0.90–1.86)	1.18 (0.89–1.36)	0.239
IgG (mg/dl)	14.32±3.29	14.64±3.54	13.61±2.61	0.321
C3 (mg/dl)	1.09±0.24	1.09±0.20	1.10±0.33	0.934
C4 (mg/dl)	0.25±0.07	0.24±0.06	0.27±0.09	0.284
D-dimer (mg/L)	0.67 (0.32–1.06)	0.57 (0.28–0.96)	0.80 (0.42–1.33)	0.130
FIB (g/L)	3.44 (2.96–4.25)	3.46 (2.94–4.22)	3.31 (2.96–4.45)	0.765
Positive antibody, n (%)				
Anti-MDA5	4 (8.0)	4 (11.4)	1 (6.7)	
Anti-NXP2	3 (6.0)	2 (5.7)	1 (6.7)	
Anti-Mi2	4 (8.0)	0 (0.0)	4 (26.7)	
Anti-TIFγ	2 (4.0)	0 (0.0)	2 (13.3)	
Anti-SRP	2 (4.0)	1 (2.9)	1 (6.7)	
Antisynthetase	21 (42.0)	21 (60.0)	0 (0.0)	
Anti-Ro-52	8 (16.0)	7 (20.0)	1 (6.7)	
Treatment, n (%)				
Treatment naïve	24 (48.0)	17 (48.6)	7 (46.7)	
Glucocorticoid	25 (50.0)	18 (51.4)	7 (46.7)	
Cyclophosphamide	1 (2.0)	1 (2.9)	0 (0.0)	
Mycophenolate mofetil	5 (10.0)	5 (14.3)	0 (0.0)	
Calcineurin inhibitor	8 (16.0)	3 (8.6)	5 (33.3)	
Janus kinase inhibitors	3 (6.0)	1 (2.9)	2 (13.3)	
Cytokines				
IL-1β (pg/mL)	82.26±9.36	83.63±9.45	79.06±8.60	0.115
IL-6 (pg/mL)	43.61 (38.35–49.72)	44.38 (38.37–49.88)	41.15 (38.28–48.93)	0.630
IL-8 (pg/mL)	199.70 (184.20–227.30)	195.50 (181.50–218.00)	222.90 (189.80–231.80)	0.138
IL-18 (pg/mL)	312.70 (294.30–334.40)	314.70 (288.00–337.40)	310.70 (302.60–330.00)	0.904
TNF-α (pg/mL)	78.79 (68.32–85.35)	78.88 (70.43–86.37)	75 (67.58–84.39)	0.937
IFN-γ (pg/mL)	748.90 (641.10–801.30)	759.30 (693.10–817.40)	662.20 (582.90–773.90)	0.021*

Notes: *$p < 0.05$.

Abbreviations: IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; PM, polymyositis; DM, dermatomyositis; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; BMI, body mass index; MMT8, manual muscle test; WBC, white blood cells; LYM, Lymphocyte; Hb, Hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; C3, complement 3; C4, complement 4; FIB, Fibrinogen.

accounting for the majority (78%). The median disease duration was 24 (IQR 5.5–48) months and the mean BMI was 23.66±3.26 kg/m^2. Among antibody-positive cases, anti-ARS antibodies were detected in 21 patients, anti-Mi-2 antibodies in 4 patients, anti-MDA5 antibodies in 4 patients, and anti-SRP antibodies in 2 patients. Anti-ARS antibodies included anti-Jo-1 (9/21), anti-EJ (5/21), anti-PL-7 (4/21), and anti-PL-12 (3/21). In addition, 8 patients tested positive for anti-Ro52 antibodies. Arthralgia was reported in 34/50 (68%) patients, myalgia in 17/50 (34%) patients, and muscular weakness in 21/50 (42%) patients. Arthritis was present in 16 (32%) patients, while Raynaud's phenomenon occurred in 6 (12%) patients. Lower extremity venous ultrasound screening revealed no cases of thrombosis.

Plasma D-Dimer and FIB Levels in IIM Patients and Their Correlation with Other Laboratory Parameters

The median plasma D-dimer in IIM patients was 0.67 mg/L, which was significantly higher than in HCs (0.19 mg/L, median, p<0.001). Similarly, the plasma FIB level was significantly elevated in IIM patients compared to controls (3.44 g/L vs 2.94 g/L, median, p=0.001) (Table 2).

According to IIM subtypes, patients were stratified into subgroups, and variations in coagulation parameters were assessed across these groups. The IMNM subgroup (n=2) was excluded from formal statistical comparisons due to insufficient sample size. Analysis of DM, PM, and ASS groups revealed significant heterogeneity in D-dimer levels by Kruskal–Wallis test (H=8.058, p=0.018). Dunn's multiple comparisons test demonstrated specifically elevated D-dimer in the DM versus ASS subgroup (1.06 mg/L vs 0.48 mg/L, median, p=0.018), whereas the PM group showed no statistically significant differences compared to either DM or ASS (all p>0.05) (Figure 1A). In contrast, Fib levels exhibited no significant intergroup variation (Kruskal–Wallis *H*-test, p=0.750) (Figure 1B).

Correlation analyses were conducted to assess the relationship between plasma coagulation markers and other disease activity laboratory parameters. Plasma D-dimer levels were positively correlated with ALT (r=0.295, p=0.037), AST (r=0.414, p = 0.003), LDH (r=0.371, p=0.008), ESR (r=0.366, p=0.009), and ferritin (r=0.421, p=0.009), while showing significant negative correlations with MMT8 score (r=−0.374, p=0.007), peripheral blood lymphocyte count (r=−0.307, p=0.030), and hemoglobin (r=−0.333, p=0.018). The plasma FIB was positively associated with CRP (r=0.440, p=0.001), ESR (r=0.456, p=0.001), and ferritin (r=0.327, p=0.049). No significant correlations were observed between coagulation markers and immunoglobulin (Table 3).

Expression of Serum Cytokines in IIM Patients

To evaluate cytokine expression profiles in IIM patients, serum levels of IL-1β, IL-6, IL-8, IL-18, TNF-α, and IFN-γ were compared between IIM patients and healthy controls. As shown in Table 2, all of these cytokines were significantly elevated in the IIM group: IL-1β (82.26±9.36 pg/mL vs 48.62±9.29 pg/mL; p<0.001), IL-6 (43.61 pg/mL vs 20.94 pg/mL, median, p<0.001), IL-8 (199.70 pg/mL vs 123.20 pg/mL, median, p<0.001), IL-18 (312.70 pg/mL vs 173.00 pg/mL,

Table 2 Comparison of D-Dimer, Fibrinogen, and Cytokines Between Idiopathic Inflammatory Myopathy (IIM) Patients and Control

	IIM, n=50	Control, n=50	p Value
Age, years	56.00±11.99	55.76±10.67	0.916
Female: Male	39:11	39:11	
D-dimer (mg/L)	0.67 (0.32–1.06)	0.19 (0.10–0.25)	<0.001*
Fibrinogen (g/L)	3.44 (2.96–4.25)	2.94 (2.61–3.20)	0.001*
IL-1β (pg/mL)	82.26±9.36	48.62±9.29	<0.001*
IL-6 (pg/mL)	43.61 (38.35–49.72)	20.94 (14.11–27.10)	<0.001*
IL-8 (pg/mL)	199.70 (184.20–227.30)	123.20 (105.80–146.30)	<0.001*
IL-18 (pg/mL)	312.70 (294.30–334.40)	173.00 (133.90–206.00)	<0.001*
TNF-α (pg/mL)	78.79 (68.32–85.35)	42.11 (33.55–51.72)	<0.001*
IFN-γ (pg/mL)	748.90 (641.10–801.30)	449.70 (343.60–507.80)	<0.001*

Notes: *p < 0.05.

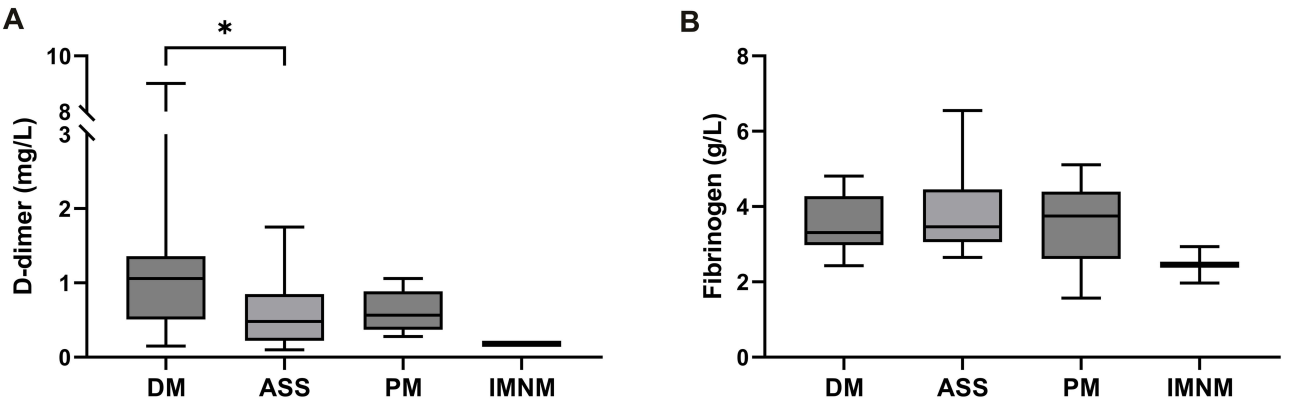

Figure 1 The levels of plasma D-dimer (**A**) and fibrinogen (**B**) in dermatomyositis (DM), antisynthetase syndrome (ASS), polymyositis (PM), and immune-mediated necrotizing myopathy (IMNM). *p < 0.05.

median, p<0.001), TNF-α (78.79 pg/mL vs 42.11 pg/mL, median, p<0.001), and IFN-γ (748.90 pg/mL vs 449.70 pg/mL, median, p<0.001).

Correlation Between Coagulation Indicators and Serum Cytokines

Spearman correlation analyses were performed to test for associations between plasma coagulation markers and cytokine levels in IIM patients. As shown in Table 3 and Figure 2A–D, plasma D-dimer levels were significantly correlated with IL-1β (r=0.325, p=0.021), IL-6 (r=0.309, p=0.029), IL-8 (r=0.347, p=0.014), and IL-18 (r=0.333, p=0.018), but showed no significant association with TNF-α and IFN-γ. No significant correlations were identified plasma FIB levels and any of the measured serum cytokines.

Comparison of Clinical Characteristics and Cytokine Levels Between IIM-ILD and IIM-Non-ILD Patients

Of the 50 IIM participants, 35 (70.00%) were diagnosed with ILD based on HRCT findings. The baseline clinical characteristics of the 35 IIM-ILD patients [DM (n = 9), PM (n = 4), ASS (n = 21), INNM (n = 1)] and the 15 IIM-non-

Table 3 Spearman Correlations Between D-Dimer, FIB, and Clinical Variables in IIM Patients

Variables	D-Dimer (mg/L)		FIB (g/L)	
	r	p-value	r	p-value
Age	0.083	0.566	−0.083	0.568
Duration	0.068	0.641	0.020	0.888
BMI	−0.034	0.814	−0.233	0.104
MMT8 score	−0.374	0.007*	−0.022	0.879
WBC (×10^9/L)	0.098	0.498	0.163	0.258
LYM (×10^9/L)	−0.307	0.030*	−0.135	0.349
Hb (g/L)	−0.333	0.018*	0.028	0.849
PLT (×10^9/L)	0.072	0.619	0.152	0.292
ALT (U/L)	0.295	0.037*	0.123	0.397
AST (U/L)	0.414	0.003*	0.197	0.170
CK (U/L)	0.028	0.846	0.088	0.546
LDH (U/L)	0.371	0.008*	0.003	0.982
CRP (mg/dl)	0.269	0.059	0.440	0.001*
ESR (mm/h)	0.366	0.009*	0.456	0.001*
Ferritin (ng/mL)	0.421	0.009*	0.327	0.049*
IgA (mg/dl)	0.059	0.691	0.227	0.121

(*Continued*)

Table 3 (Continued).

Variables	D-Dimer (mg/L)		FIB (g/L)	
	r	p-value	r	p-value
IgM (mg/dl)	−0.114	0.439	−0.165	0.263
IgG (mg/dl)	−0.066	0.654	0.260	0.075
C3 (mg/dl)	0.122	0.455	0.266	0.098
C4 (mg/dl)	0.224	0.164	0.187	0.248
IL-1β (pg/mL)	0.325	0.021*	0.137	0.344
IL-6 (pg/mL)	0.309	0.029*	0.195	0.174
IL-8 (pg/mL)	0.347	0.014*	0.003	0.982
IL-18 (pg/mL)	0.333	0.018*	0.204	0.156
TNF-α (pg/mL)	−0.033	0.819	0.114	0.431
IFN-γ (pg/mL)	0.025	0.861	−0.091	0.529

Notes: *p < 0.05.

Abbreviations: FIB, Fibrinogen; IIM, idiopathic inflammatory myopathy; BMI, body mass index; MMT8, manual muscle test; WBC, white blood cells; LYM, Lymphocyte; Hb, Hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; C3, complement 3; C4, complement 4.

ILD patients [DM (n = 12), PM (n = 2) and INNM (n = 1)] are summarized in Table 1. There were no significant differences between the two subgroups in terms of gender, age, disease duration, or BMI. The frequency of arthralgia, myalgia, arthralgia, and Raynaud's phenomenon in the ILD group was also not significantly different between the groups (p>0.05). MMT8 score was significantly higher in the IIM-ILD group compared to the IIM-non-ILD group (p=0.028), while serum LDH levels was markedly lower in the IIM-ILD group (p=0.011); however, plasma D-dimer (Figure 2E) and FIB levels showed no significant differences between the two subgroups. In contrast, IFN-γ levels were significantly higher in IIM-ILD patients compared to those without ILD (759.30 pg/mL vs 662.20 pg/mL, median, p=0.022)

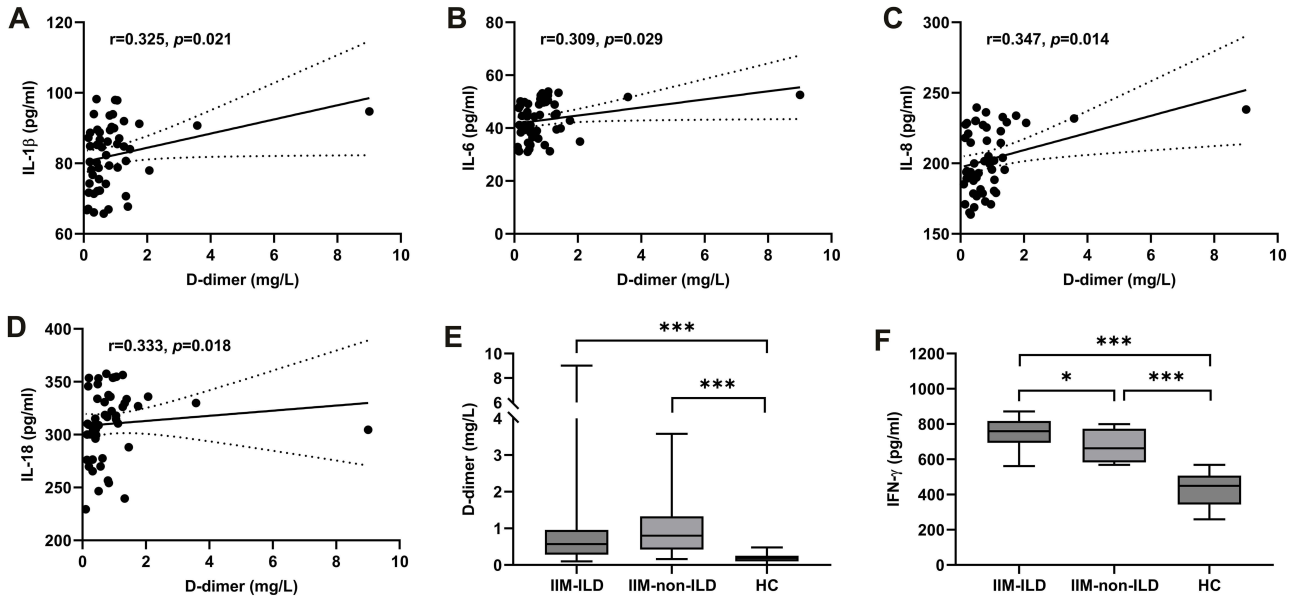

Figure 2 Spearman correlation of serum IL-1 (**A**), IL-6 (**B**), IL-8 (**C**), and IL-18 (**D**) versus plasma D-dimer in idiopathic inflammatory myopathy (IIM) patients. The levels of plasma D-dimer (**E**) and serum IFN-γ (**F**) in IIM-interstitial lung disease (ILD), IIM-non-ILD, and control individuals (HCs). *p < 0.05, ***p < 0.001.

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(Figure 2F). No statistically significant differences were observed between the two subgroups in IL-1β, IL-6, IL-8, IL-18, or TNF-α (Table 1).

Discussion

This study found that plasma D-dimer and FIB levels were significantly elevated in IIM patients compared to healthy controls, and that these coagulation markers correlated positively with indicators of IIM disease activity, including ferritin and ESR. The analysis of IIM subtypes revealed significantly higher D-dimer levels in the DM group compared to the ASS group. Additionally, serum levels of IL-1β, IL-6, IL-8, IL-18, TNF-α, and IFN-γ were significantly higher in IIM patients. Correlation analysis demonstrated that D-dimer was positively associated with IL-1β, IL-6, IL-8, and IL-18, suggesting a relationship between coagulation and inflammation in IIM. In subgroup analyses, MMT8 score and IFN-γ levels were significantly elevated in IIM patients with ILD compared to those without ILD, and serum LDH levels were significantly lower, while no significant differences were identified in D-dimer or FIB levels between these two subgroups.

ALT, AST, and LDH are elevated in response to muscle injury and are considered indicators of IIM disease activity.[16,17] ESR, CRP and serum ferritin are all acute phase proteins commonly used to assess disease activity in autoimmune and inflammatory diseases. Serum ferritin is a key marker of inflammation and macrophage activation,[18,19] and its elevation has been associated with the development and progression of acute ILD in DM.[20] Peripheral blood lymphocyte count has also been associated with IIM severity, with lower counts linked to more severe disease.[21,22] In this study, plasma D-dimer was significantly positively correlated with ALT, AST, LDH, ESR, and ferritin and negatively correlated with MMT8 score and peripheral blood lymphocyte count. FIB was significantly positively correlated with CRP, ESR, and ferritin. These findings suggest that D-dimer and FIB may serve as serological markers of IIM disease activity. Given that these markers are routinely measured in the clinic, minimally invasive, and cost-effective, dynamic monitoring of their levels may aid clinicians in assessing IIM disease progression, treatment response, and prognosis. Despite the observed increases in D-dimer and FIB levels, we did not observe a higher incidence of thromboembolic events in IIM patients, suggesting that these increases are more likely related to hyperfibrinolysis secondary to chronic inflammation rather than an increased risk of thrombosis. As such, we speculate that anti-inflammatory treatment may be more critical than anticoagulation therapy in IIM patients with elevated D-dimer or FIB levels. Our findings demonstrate significantly elevated D-dimer levels in the DM subgroup compared to other IIM subtypes, indicating a greater degree of vascular endothelial involvement and an increased proclivity for microthrombosis in DM.[23]

Cytokines are key mediators of inflammation and immune regulation, and are considered potential biomarkers of IIM.[5] They are produced by various cell types and exert both pro-inflammatory and anti-inflammatory effects, with pro-inflammatory cytokines playing a particularly important role in the pathogenesis of IIM. Studies have demonstrated significantly elevated IL-1β expression in IBM, PM, and DM muscle tissue compared to controls.[24,25] Previous studies have reported that serum IL-6 and IL-8 levels are significantly increased in patients with myositis and correlate positively with disease activity.[7,26] Hidenaga et al further demonstrated that IL-6 and IL-8 are associated with hyperferritinemia in RP-ILD with PM/DM.[27] Evidence suggests that IL-18 is up-regulated in the muscle and serum of DM patients and correlates with disease activity and ILD.[28–30] IL-18 may play a key role in the development of anti-MDA5-associated ILD. TNF-α, which is primarily produced by macrophages, is a pleiotropic cytokine that induces the synthesis of IL-1, stimulates the phagocytosis of lymphocytes, upregulates major histocompatibility complex (MHC)-I and II expression, and strongly up-regulates intercellular cell adhesion molecule (ICAM)-1 expression in human skeletal muscle cells.[31] IFN-γ, secreted by activated T cells, selectively promotes Th1 immune responses and is a potent stimulator of MHC-I expression. It up-regulates MHC-I on muscle fibers and induces the production of pro-inflammatory cytokines and chemokines. IFN-γ also strongly stimulates macrophages to develop a pro-inflammatory phenotype by inducing the synthesis of pro-inflammatory cytokines, increasing phagocytosis and antigen-presenting capacity, and promoting the synthesis of reactive oxygen species.[32] Evidence suggests that IFN-γ-producing resident macrophages play an important role in the pathogenesis of RP-ILD.[33] In this study, serum levels of IL-1β, IL-6, IL-8, IL-18, TNF-α, IFN-γ were significantly elevated in IIM patients compared to healthy controls, suggesting that these cytokines may play a central role in IIM pathogenesis, consistent with previous findings.

Studies have shown that coagulation markers such as D-dimer can influence the release of inflammatory cytokines. D-dimer has been demonstrated to promote monocyte synthesis and the release of biologically active IL-1β and IL-6.[34] Meanwhile, accumulated evidence indicates that inflammatory markers such as IL-1β, IL-6, and IL-8 contribute to coagulation and fibrinolysis. Elevated cytokine and chemokine levels can trigger endothelial activation, endothelial cell damage, increased platelet aggregation, heightened thrombin sensitivity, and the recruitment and activation of leukocytes within the vascular wall. These processes eventually promote thrombin and fibrin formation at the local level.[35] IL-6 and IL-8 may directly damage endothelial cells, increase the synthesis and release of von Willebrand factor (vWF) in endothelial cells, and promote the adhesion of platelets, white blood cells, and vascular endothelial cells.[36,37] Vinita et al demonstrated that IL-1β influences coagulation via several mechanisms, including leukocyte recruitment, thrombogenic microparticle signaling, and platelet integrin activation.[38] Li et al found that IL-18 can modify the proliferation and apoptosis of endothelial cells by activating the NF-κB-mediated signaling pathway, resulting in endothelial dysfunction abnormal regulation of coagulation factors, such as vWF, P-selectin, and tissue type PA (t-PA).[39] In this study, IL-1β, IL-6, IL-8, and IL-18 were positively correlated with plasma D-dimer levels in patients with IIM. These findings suggest that elevated levels of these cytokines may contribute to increased D-dimer levels by activating the coagulation cascade. In addition, D-dimer itself may further promote the release of cytokines by stimulating inflammatory signaling, creating a vicious cycle of inflammation and coagulation, and thus representing a key mechanism for the persistence of IIM disease activity.

ILD is a clinically significant complication of IIM and is associated with an unfavorable prognosis. In this study, there were no significant differences in D-dimer and FIB levels between IIM patients with and without ILD, suggesting that the pathogenesis of ILD in IIM involves mechanisms that are beyond endothelial injury. However, serum IFN-γ levels were significantly higher in IIM patients with ILD, suggesting that IFN-γ may contribute to ILD development and progression. IFN-γ has been shown to promote pulmonary inflammation and fibrosis through the induction of a pro-inflammatory macrophage phenotype. Previous studies have shown that LDH levels are negatively correlated with ILD in DM/PM and patients with serum LDH levels above 400 U/L have a lower incidence of ILD.[40] However, inconsistencies exist among published reports. Other studies have found that LDH levels are higher in ILD patients compared to non-ILD patients with DM.[41] It has been suggested that IIM exists along a clinical and pathophysiological spectrum, where some patients exhibit predominant muscle and minimal extramuscular involvement, while others present with less muscle involvement and more extensive skin and lung involvement.[42] This spectrum model provides a plausible explanation for our observation that IIM patients with ILD demonstrated significantly higher MMT8 scores (indicating better muscle strength) compared to those without ILD.

There are several limitations to this study. First, it was a single-center study with a relatively small sample size, which might introduce some selection bias. Second, different subtypes of IIM were combined in the analysis, despite potential differences in the underlying pathophysiology. Third, due to study design and constraints related to patient follow-up, myositis activity assessment tools were not utilized to evaluate disease severity. Fourth, the selective thrombosis evaluation protocol (limited to patients with abnormal coagulation markers) represents a potential detection bias for asymptomatic cases.

Conclusion

In conclusion, this study demonstrated that plasma D-dimer, FIB, and inflammatory cytokines were elevated in IIM patients, with D-dimer levels significantly correlating with serum IL-1β, IL-6, IL-8, and IL-18. Plasma D-dimer and FIB were correlated with markers of disease activity, including inflammatory markers and muscle enzymes, suggesting that coagulation indicators may serve as potential biomarkers of disease severity in IIM. Inflammatory cytokines appear to play an important role in promoting a hypercoagulable state in IIM patients. Our findings highlight the clinical significance of coagulation markers and inflammatory mediators in evaluating disease progression. We recommend larger multi-center studies to validate our clinical findings and in vitro and in vivo studies to investigate the mechanistic links between inflammation and coagulation in IIM.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study protocol was approved by the Ethics Committee of Jining No. 1 People's Hospital (reference number 2022-LLY-035). All participants provided written informed consent. The study was performed according to the ethical principles of the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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