Decreased low-density lipoprotein and the presence of pulmonary arterial hypertension among newly diagnosed drug-naïve patients with systemic lupus erythematosus: D-dimer as a mediator

JING HUANG[1], QI AN[1], CAI-LIAN ZHANG[2], LAN HE[1] and LEI WANG[3]

[1]Department of Rheumatism and Immunology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061; [2]Department of Pulmonary and Critical Care Medicine, Yan'an University Affiliated Hospital, Yan'an, Shaanxi 716000; [3]Department of Pulmonary and Critical Care Medicine, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710004, P.R. China

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Abstract. Pulmonary arterial hypertension (PAH) is commonly associated with systemic lupus erythematosus (SLE). The present study investigated the relationship between coagulation and changes in lipid parameters in newly-diagnosed patients with SLE in the presence of PAH and whether the coagulation parameters were mediators between lipids and PAH presence. A total of 301 subjects scheduled for new-onset drug-naïve SLE were consecutively enrolled. Baseline data for patients without PAH and with PAH were gathered and compared. Coagulation and lipid parameters were compared across patients without lipid regulating and anticoagulation medications. Multivariable logistic regression model was applied to examine potential predictors of PAH in SLE. The relationships between them were examined using Spearman's correlation analysis. The relationship between coagulation index and lipids with SLE-PAH was evaluated using mediation analysis. Female patients accounted for 88.0% of the 301 subjects, and the average age was 32 years (range, 25-45 years). A total of 40 patients (13.3%) had PAH, and the average pulmonary artery systolic pressure (sPAP) was 55.825±26.67 mmHg. Patients with PAH were older and had higher levels of fibrin/fibrinogen degradation products (FDP), D-dimer, C-reactive protein, lower levels of complement 3, complement 4 and 25-hydroxy vitamin D3 compared with the non-PAH group. Multivariable logistic regression analysis showed that age and D-dimer were independent predictor factors for PAH. Among patients without lipid regulating and anticoagulation medications, patients in the PAH group had higher levels of D-dimer and FDP, and lower low-density lipoprotein (LDL) levels compared with patients without PAH. There was also a positive relationship between sPAP and D-dimer and FDP, and a negative relationship between sPAP and total cholesterol and LDL. Mediation analysis indicated that 25.61% of the effect of low LDL on PAH presence in systemic lupus erythematosus was mediated by D-dimer. Overall, the effect of low LDL on SLE-PAH appeared to be mediated by D-dimer, which mediated 25.61% of this effect.

Correspondence to: Dr Lei Wang, Department of Pulmonary and Critical Care Medicine, Second Affiliated Hospital of Xi'an Jiaotong University, 157 Xiwu Road, Xin Cheng, Xi'an, Shaanxi 710004, P.R. China
E-mail: wl860806wb@163.com

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SLE, systemic lupus erythematosus; sPAP, pulmonary artery systolic pressure; FDP, fibrin/fibrinogen degradation products; FIB, fibrinogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; C3, complement 3; C4, complement 4; 25(OH) D_3, 25-hydroxy vitamin D3; LDL, low-density lipoprotein; TC, total cholesterol; CTDs, connective tissue diseases; HDL, high-density lipoprotein; SLEDAI, systemic lupus erythematosus disease activity index; RHC, right heart catheterizations

Key words: lipid, low-density lipoprotein, D-dimer, new-onset, systemic lupus erythematosus-pulmonary arterial hypertension, mediation analysis

Introduction

Pulmonary hypertension (PH) affects ~1% of global population, with 80% of cases being reported in developing countries (1). Heart and lung diseases are the most frequent causes leading to PH (2). Connective tissue diseases (CTDs) have also been associated with PH (1).

Pulmonary arterial hypertension (PAH) is a serious complication and major cause of morbidity and mortality in patients with CTDs (3). Approximately 30% of scleroderma-related deaths are due to PAH (4). In contrast to Western countries, epidemiological studies performed in Asian countries, including Korea, Japan and China, have revealed that systemic lupus erythematosus (SLE) is the main cause of PAH among patients with CTDs instead of systemic sclerosis (5-7). Moreover, the Chinese SLE Treatment and Research group (CSTAR) registry revealed that the possible prevalence of PAH in patients with SLE was 3.8% (8). Chen *et al* (9) demonstrated

that the average interval from SLE diagnosis to PAH diagnosis is 3.66 years, and that 70% of patients with SLE develop PAH within 5 years of disease onset. However, the presence of PAH in patients with new-onset SLE and the potential predictors remains to be studied.

Abnormal lipid metabolism participates in the pathogenesis of PH (10). In patients with PH, the levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are decreased (11-13). Thus, HDL and LDL have been suggested as markers for prediction and assessment of PH (11,14). In addition, a study suggested that inflammation triggered by CTDs can lead to dysregulation of lipid metabolism (15). Nonetheless, the exact relationship between lipid biomarker and CTDs-PAH remains unclear.

Thrombosis is one of the possible etiologies of PH, and several coagulation indices are associated with PH. For example, high plasma fibrinogen has been suggested as an independent predictor of survival in patients with chronic thromboembolic pulmonary hypertension (16). Although endogenous fibrinolysis may be involved in the pathophysiology of PH, the role of D-dimer, a fibrin degradation product, in PH remains controversial. A previous study found significantly high D-dimer levels in primary pulmonary hypertension (17). It was also reported that D-dimmer level is not associated with pulmonary artery pressure in patients with systemic sclerosis (18). Lipids can affect coagulation and fibrinolytic factors (19). However, the role of coagulation indices in the PH needs to be further clarified, especially in CTDs-PAH. Furthermore, if coagulation mediates the effect of lipids in CTDs-PAH is also unclear. Therefore, in the present study, the relationship between coagulation and lipids biomarkers in newly diagnosed patients with SLE and PAH was investigated, and whether the coagulation parameters showed mediating effect on the association between lipids and PAH presence.

Materials and methods

Study design and population. Newly diagnosed, untreated patients with SLE admitted to the Rheumatology and Immunology Department at the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) between January 2019 and December 2020 were retrospectively collected. All patients underwent routine echocardiography examinations during hospitalization. The 1997 updated American College of Rheumatology criteria for SLE was applied to diagnose SLE. Patients with other connective tissue diseases, such as left heart disease, antiphospholipid syndrome, congenital heart disease, valvular heart disease, HIV and portal hypertension were excluded. Finally, 301 patients with SLE who met these criteria were included in the analyses (20).

The Ethics Committee of First Affiliated Hospital of Xi'an Jiaotong University (approval no. 2022-291) approved the study, which was conducted according to the Declaration of Helsinki. Written informed consent were provided by all patients.

Clinical and laboratory data collection. Baseline characteristics (age, sex, smoking habit and systemic blood pressure), laboratory tests, systemic lupus erythematosus disease activity index (SLEDAI), medications and history of thrombosis events were obtained from electronic medical records.

Echocardiographic evaluation. Doppler echocardiogram, as a routine examination, was performed on each admitted patient to screen for the presence of PH. Pulmonary artery systolic pressure (sPAP) was estimated adopting a modified Bernoulli equation (21): sPAP=4 x (tricuspid systolic jet)^2 + 10 mmHg (estimated right atrial pressure). PH was defined as an estimated sPAH >35 mmHg using echocardiograms.

Statistical analysis. Continuous variables are presented as mean ± standard deviation if normally distributed proved by Kolmogorov-Smirnov test, otherwise data are presented as median and interquartile range (IQR). Categorical variables are presented as counts and proportions. Demographic characteristics and relevant risk factors were compared between PAH and no PAH groups using independent samples t-tests or Wilcoxon rank-sum tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Spearman's correlation analyses were used to examine the relationships between coagulation and lipid index with SLE disease activity and sPA. A multivariable logistic regression model was built to examine potential PAH predictors.

To test if coagulation is a mediator between lipids and PAH, package 'mediation' in R Studio (version 1.2.5001) was utilized to conduct causal mediation analysis in applied empirical research (https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf) (22). A mediator variable is a variable that causes mediation in the dependent (PAH) and the independent variables (lipids). Therefore, it explains the relationship between the dependent variable and the independent variable (23,24).

All analyses were performed using SAS 9.4 software (Cary) and RStudio version 1.2.5001 (RStudio, Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients' characteristics. A total of 301 newly diagnosed, untreated patients with SLE were identified during the study period. Female patients accounted for 88.0% of the sample, and the average age was 32 years (range, 25-45 years). A total of 40 patients (13.3%) demonstrated PAH after doppler echocardiogram examination. The average sPAP was 55.825±26.67 mmHg (range 35-156 mmHg).

Patients were divided into two groups: Non-PAH and PAH groups. There was no significative difference in sex, BMI, systemic blood pressure, smoking habits, and kidney function between the two groups (Fig. 1A; Table I). However, patients in the PAH group were older and had higher levels of D-dimer, FDP, C-reactive protein (CRP), lower levels of complement 3 (C3), complement 4 (C4) and 25-hydroxy vitamin D_3 ($25(OH)D_3$) compared with the non-PAH group. In addition, a higher number of patients in the PAH group used lipid regulating, anticoagulation and antiplatelet medications compared with the non-PAH group (Fig. 1B). Moreover, a higher number of arterial and venous thrombosis events were recorded in the PAH group compared with the non-PAH group; however, there was no statistical difference (Fig. 1C).

Table I. Characteristics of study subjects.

Characteristics	Non-PAH (n=261)	PAH (n=40)	P-value
Sex [male; (%)]	31.00 (11.88%)	5.00 (12.50%)	1.00
Median age, years (IQR)	31.00 (25.00-44.00)	39 (29.00-49.00)	0.02
Median BMI, kg/m^2 (IQR)	20.20 (17.90-22.31)	19.67 (18.00-27.25)	0.72
Median SBP, mmHg (IQR)	113.00 (102.00-122.00)	113.00 (107.00-123.50)	0.40
Median DBP, mmHg (IQR)	76.00 (68.00-81.00)	75.00 (67.50-83.50)	0.91
Smoke, n (%)	15.00 (5.75%)	2.00 (5.00%)	1.00
Median FIB, g/l (IQR)	3.21 (2.62-3.91)	2.97 (2.11-3.87)	0.12
Median DD, mg/l (IQR)	1.30 (0.60-2.60)	2.00 (0.95-4.26)	0.01
Median APTT, s (IQR)	37.70 (34.10-41.95)	37.15 (35.60-43.20)	0.63
Median FDP, mg/l (IQR)	3.60 (1.57-7.14)	5.84 (3.20-11.40)	0.01
Median 24UTP, g (IQR)	0.13 (0.05-0.48)	0.23 (0.09-1.05)	0.13
Median Cr, μmol/l (IQR)	49.00 (41.00-60.00)	54.00 (40.00-60.00)	0.66
Median BUN, mmol/l (IQR)	4.65 (3.60-6.38)	5.24 (3.28-6.91)	0.47
Median uric acid, μmol/l (IQR)	283.66 (224.50, 370.50)	325.00 (225.00-423.00)	0.13
Median eGFR, ml/min/1.73^2 (IQR)	136.29 (109.63-170.44)	123.45 (97.97-141.92)	0.21
Median C3, g/l (IQR)	0.58 (0.34-0.79)	0.38 (0.30-0.66)	0.04
Median C4, g/l (IQR)	0.09 (0.06-0.16)	0.07 (0.05-0.09)	0.01
Median dsDNA, IU/ml (IQR)	2.50 (1.00-25.50)	2.00 (1.00-14.00)	0.84
Median SLEDAI (IQR)	9.00 (6.00-15.00)	12.00 (8.00-16.00)	0.10
Median ESR, mm/h (IQR)	45.00 (23.00-77.00)	61.00 (23.00-80.00)	0.35
Median CRP, mmol/l (IQR)	4.70 (3.00-11.90)	10.00 (4.40-20.10)	0.01
Median total cholesterol, mmol/l (IQR)	3.28 (2.72-3.81)	3.21 (2.53-3.95)	0.40
Median triglyceride, mmol/l (IQR)	1.46 (1.02-2.23)	1.44 (1.12-2.15)	0.97
Median LDL, mmol/l (IQR)	1.87 (1.45-2.35)	1.60 (1.30-2.15)	0.12
Median HDL, mmol/l (IQR)	0.71 (0.57-0.90)	0.70 (0.48-0.89)	0.36
Median 25(OH)D_3, ng/ml (IQR)	10.60 (6.80-15.20)	8.30 (6.40-11.20)	0.02

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FIB, fibrinogen; DD, D-dimer blood test; APTT, activated partial thromboplastin time; FDP, fibrin degradation products; 24UTP, 24-h urine protein; Cr, creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; C3, complement 3; C4, complement 4; dsDNA, double stranded DNA; SLEDAI, systemic lupus erythematosus disease activity index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; 25(OH)D_3, 25-hydroxy vitamin D3; PAH, pulmonary arterial hypertension.

Predictors of PAH in patients with SLE. To examine potential predictors of PAH in patients with SLE, a multivariable logistic regression model was constructed. The age and D-dimer were independent predictor factors for PAH (Table II).

Table II. Multivariable logistic regression model for predictors of PAH presence.

Risk factors	OR with 95% CI	P-value
Age, 1 unit increase	1.03 (1.01, 1.06)	0.0092
DD, 1 unit increase	1.10 (1.02, 1.18)	0.0132

PAH, pulmonary arterial hypertension; DD, D-dimer; OR, odds ratio.

Coagulation and lipid parameters in patients with SLE-PAH. In order to further analyze coagulation and lipid parameters in patients with SLE-PAH, medical records were examined from 221 patients not using lipid regulating or anticoagulation medications among the 301 subjects. A total of 19 patients presented PAH and the average sPAP was 53.26±23.49 mmHg. Patients in the PAH group had higher D-dimer and FDP levels, as well as significantly lower LDL levels compared with the non-PAH group (Fig. 2).

Association of coagulation and lipid index with SLE disease activity and PAH. The relationship of coagulation and lipid index with SLE disease activity and PAH was analyzed in patients with no records of lipid regulating and anticoagulation medications (Fig. 3). No association was found among anti-double-stranded (ds)-DNA, coagulation (FIB, D-dimer and FDP) and lipid index (TG, TC, LDL and HDL). SLEDAI was positively associated with D-dimer and FDP and negatively associated with total cholesterol (TC) and HDL. C3 and C4 were negatively associated with D-dimer and FDP, and positively associated with HDL. The coagulation index was

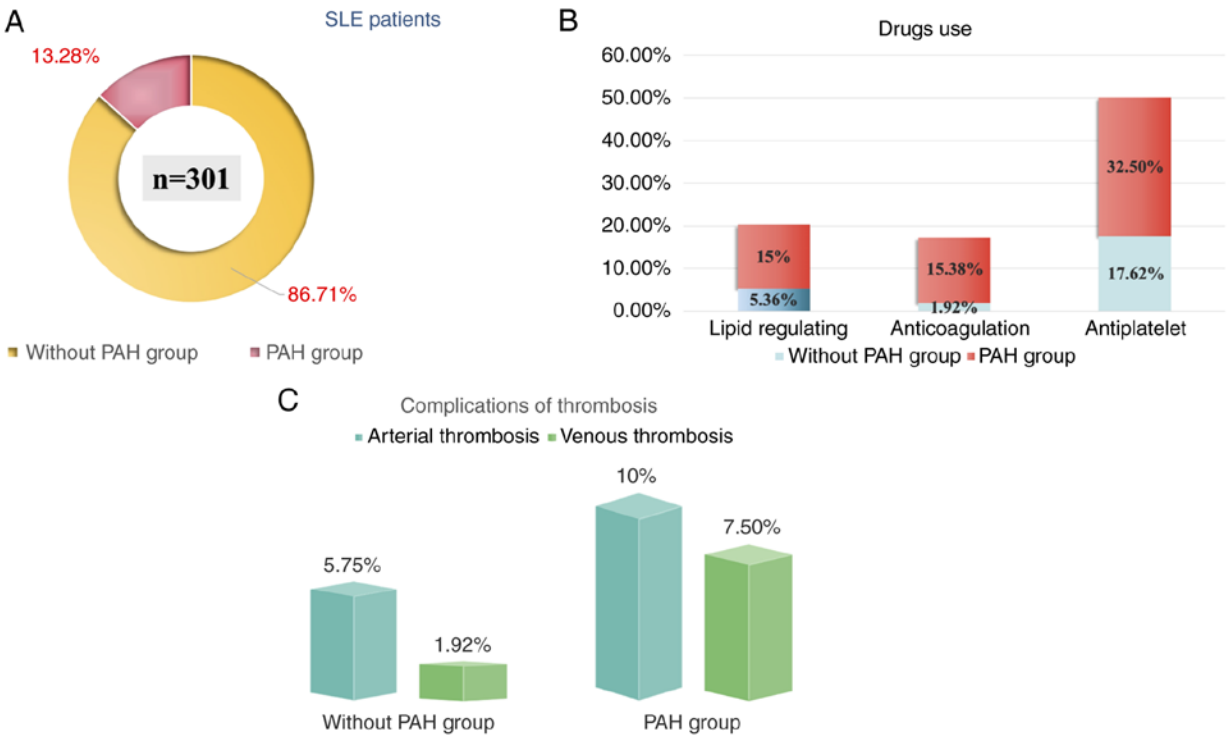

Figure 1. Characteristics of patients with SLE. (A) Proportion of patients with PAH. (B) Lipid regulating, anti-coagulation and anti-platelet drugs usage. (C) Thrombosis complications. SLE, systemic lupus erythematosus; PAH, pulmonary arterial hypertension.

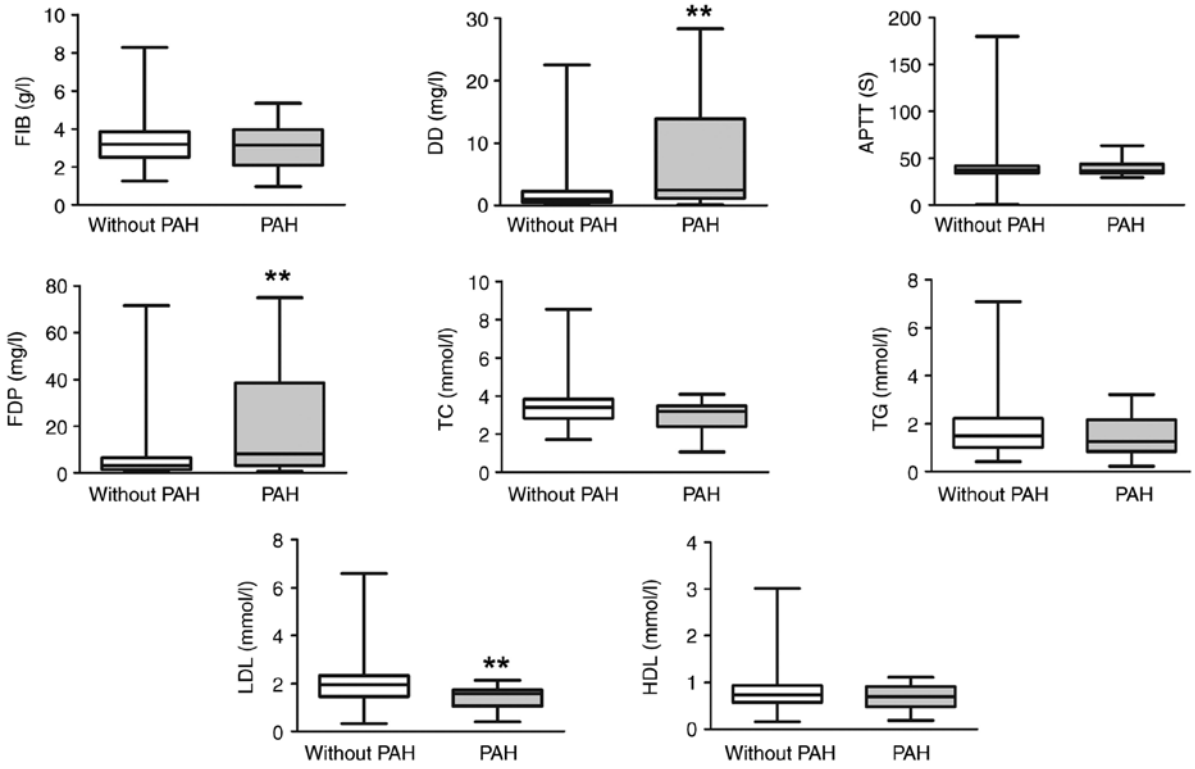

Figure 2. Coagulation and lipid index between patients with PAH and without PAH without medications. **P<0.01 vs. without PAH. FIB, fibrinogen; DD, D-dimer blood test; APTT, activated partial thromboplastin time; FDP, fibrin degradation products; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PAH, pulmonary arterial hypertension.

positively associated with inflammatory markers erythrocyte sedimentation rate (ESR) and CRP. Moreover, no significant association was found among lipid index, ESR and CRP. For PAH, there was a positive association between sPAP and D-dimer and FDP, and a negative association among sPAP, TC and LDL.

Table III. Mediation analysis of DD and FDP for the association of lipid index with PAH.

	PAH		
Mediator	Item	Coefficient β	P-value
DD	Total effect of TC	-1.600	0.024
	Effect mediated by DD	-0.296	0.128
	Effect no mediated by DD	-1.303	0.044
	Proportion of mediation	0.185	
	Total effect of LDL	-2.311	<0.001
	Effect mediated by DD	-0.592	0.024
	Effect no mediated by DD	-1.719	0.032
	Proportion of mediation	0.256	
FDP	Total effect of TC	-1.600	0.008
	Effect mediated by FDP	-0.251	0.160
	Effect no mediated by FDP	-1.349	0.024
	Proportion of mediation	0.157	
	Total effect of LDL	-2.312	<0.001
	Effect mediated by FDP	-0.480	0.088
	Effect no mediated by FDP	-1.832	0.004
	Proportion of mediation	0.207	

PAH, pulmonary arterial hypertension; FDP fibrin/fibrinogen degradation products; DD, D-dimer; TC, total cholesterol; LDL, low-density lipoprotein.

Mediation effects of D-dimer for the association between LDL and PAH. As aforementioned, patients with PAH had higher levels of D-dimer and FDP and a lower LDL level compared with the non-PAH group, and sPAP had a positive association with D-dimer and FDP and a negative association with TC and LDL. Therefore, mediation analyses were performed with D-dimer and FDP as potential mediators for the associations of TC, LDL with the presence of PAH (Table III). In the present model, PAH presence was the dependent variable, the TC and LDL levels were the independent variable, and D-dimer and FDP were the mediator variables. For patients with no records of lipid regulating and anticoagulation medications, data indicated that the relationship between lower LDL and PAH presence was partially mediated by D-dimer. Mediation analysis indicated that 25.61% of the effect of low LDL on the presence of PAH in SLE was mediated by D-dimer. No other mediation effects were found.

Discussion

To the best of our knowledge, the present study is the first to report the association between coagulation index and lipids with PAH. The novel finding of the present study is that the effect of low LDL on SLE-PAH could mediated by D-dimer, which mediated 25.61% of this effect.

Mortality remains relatively high in patients with SLE and PAH (25). Cohort studies have reported that the prevalence of PAH ranges from 0.5 to 43% in SLE (8). However, a previous study estimated a lower prevalence of PAH (2.54%) (26). Johnson *et al* (27) found a prevalence of 14% in patients with systemic lupus who underwent transthoracic echocardiogram. In the present study, the prevalence of PAH in newly diagnosed drug-naive patients with SLE was 13.3%. PAH can be an initial presentation of SLE, including severe PAH (28). Moreover, in the present study sPAP could reach 156 mmHg. Since the presence of PAH indicates a worse prognosis in patients with SLE, prompt recognition and early initiation of PAH treatment are extremely important.

Previous studies showed that Raynaud's phenomenon, pleuritis, pericarditis, disease duration, interstitial lung disease, anti-RNP antibodies, anti-SSA/Ro antibodies and anticardiolipin antibodies are independent predictors of PAH in systemic lupus erythematosus (29). In the present study, age and D-dimer were independently associated with the development of PAH in SLE. In the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management with right heart catheterizations (RHC) confirmed SLE-PAH, the mean age at the time of the PAH diagnosis was ~45 years (45.5±11.9 years) (30). In the present study, PAH presented at a younger age (~39 years; range 28.5-49 years), and the risk of PAH increased with the patient's age. The Chinese CSTAR-PAH registry study revealed a case of SLE-PAH at a younger age (35.3±10.3 years) (31). Thus, it is recommended to screen for PAH soon after SLE diagnosis.

A previous study found an increased level of D-dimer in patients with active SLE (32). Moreover, the hypercoagulable state is also considered a contributor in the development of PAH in SLE (33). High fibrinogen and D-dimer levels are found in SLE-PAH patients (33). In the present study, patients with SLE-PAH had high D-dimer and FDP levels, and D-dimer was an independent predictor for SLE-PAH. The changes in thrombogenic risk factors are thought to be the rationale for

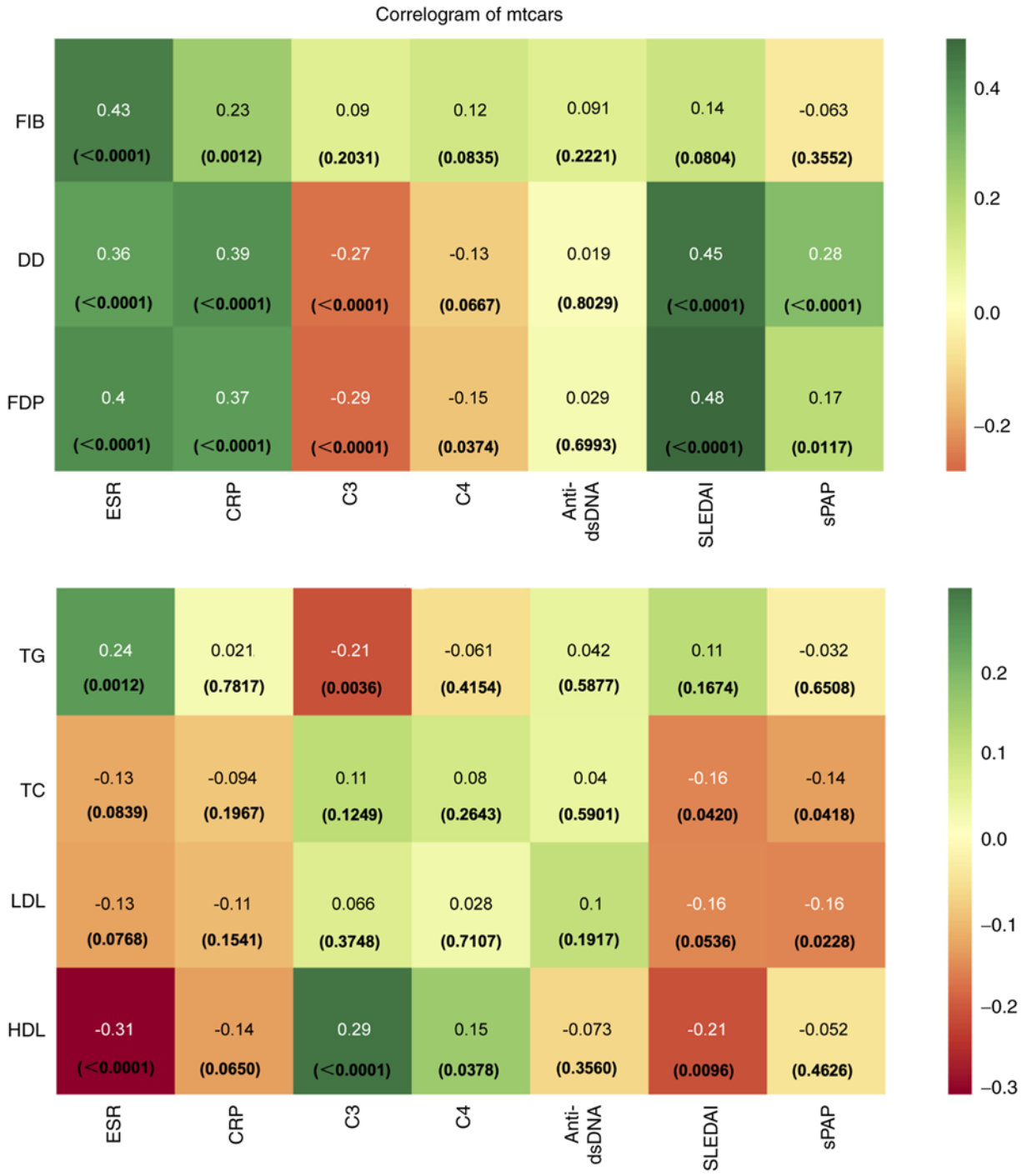

Figure 3. Correlogram of Mtcars dataset of this study. Presents the degree of correlation between coagulation/lipid index and SLE disease activity/sPAP. No correlation is shown in white, positive correlation in green, and negative correlation in orange. Darker color indicates higher absolute value of the correlation. SLE, systemic lupus erythematosus; sPAP, pulmonary artery systolic pressure; FIB, fibrinogen; DD, D-dimer blood test; FDP, fibrin degradation products; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; C3, complement 3; C4, complement 4; dsDNA, double stranded DNA; SLEDAI, systemic lupus erythematosus disease activity index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride.

using oral anticoagulation in patients with SLE-PAH as a management strategy.

Lipid metabolism is important during cellular metabolism and effective immune responses. Dyslipidemia contributes to disease pathogenesis and associated comorbidities in autoimmune rheumatic diseases including SLE (34). Increased cardiovascular disease (CVD) risk in autoimmune diseases is related to dyslipidemia (35). Previous data showed that dyslipidemia is a major factor in the progression of CVD in SLE (36), but whether dyslipidemia is associated with PAH in patients with SLE remains unclear. Lipid homeostasis is dysregulated in patients with PH in which low HDL and LDL levels have been found (11,37,38); therefore, their anti-inflammatory properties may be relevant for predicting disease severity and prognosis in patients with PH, and the decreased HDL and LDL levels is also associated with the right heart function in patients with idiopathic PAH (39). Wang *et al* (13) found that the optimal cutoff value of the serum HDL concentration for

predicting PAH was 1.32 mmol/l. Moreover, it remains unclear if cholesterol levels are altered in patients with SLE-PAH. Nonetheless, the results of the present study demonstrated decreased LDL level in the development of PAH in patients with SLE. In the present study, LDL was negatively associated with pulmonary artery pressure. Reduced LDL levels have also been represented in other chronic diseases such as rheumatoid arthritis (40), cancer diseases (41), end-stage renal failure (42) or chronic heart failure (43). However, the exact mechanisms accounting for the association between low LDL and PAH have not been fully understood. To the best of our knowledge, the present study is the first reporting changes in LDL levels in patients with SLE-PAH. This may be due to chronic inflammatory condition (44), malnutrition (45) and altered liver metabolism (46) in patients with SLE-PAH. The present study showed that the relationship between low LDL and occurrence of PAH in SLE is partially mediated by D-dimer. Nevertheless, the potential molecular mechanisms need to be further investigated.

To the best of our knowledge, the potential mechanisms by which low LDL affects PH, including SLE-PAH, have not been clarified. Limited basic research data suggest that LDL receptor is downregulated in the lung tissue of patients with PH, while LDL receptor knockout mice can develop PH; in addition, LDL receptor knockdown significantly increases proliferation of human pulmonary artery smooth muscle cells *in vitro* (47). However, the potential molecular mechanisms have not been clarified, which need more related basic researches.

The strength of the present study is that the intermediary variable D-dimer is first used to connect the relationship between dyslipidemia and PAH in SLE. The present cohort study included newly diagnosed drug-naïve patients, whereas patients using lipid-lowering/anticoagulant were excluded to minimize the effect of possible confounding factors. To the best of our knowledge, the present results demonstrated for the first time that LDL could affect the PAH severity via D-dimer in patients with SLE. The present study also has several limitations. First of all, no measurements through RHC were made to quantify pulmonary artery pressure. Nonetheless, considering the invasive nature of RHC, indirect echocardiography was used to estimate pulmonary artery systolic pressure. Although Doppler echocardiography is widely accepted as a screening tool in PH, it has certain limitations. A higher discrepancy between echocardiographic and RHC data has been reported (48). Secondly, the present study is cross-sectional, therefore it is difficult to identify the causal or temporal relationship between LDL levels and the presence of PAH in SLE. Follow-up is needed to clarify whether LDL level is associated with PH progression and patients' prognosis. Thirdly, the present study had a relatively small sample size. Lastly, the present study did not explore the exact molecular mechanisms of the interplay between coagulation index and lipids.

Early recognition of PAH in patients with SLE is of utmost importance for patient' prognosis. The present data indicated that the effect of low LDL on SLE-PAH may be mediated by D-dimer, which mediated 25.61% of this effect. Dynamic monitoring and regulation of lipids would be important in the PAH early recognition, treatment and prognosis prediction in patients with SLE, while lipid modulation may achieve additional benefits to the management of patients with SLE-PAH. Further studies are necessary to explore the underlying mechanisms of this apparent association and the mediation effect.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LW, LH and JH conceived the study design. JH, QA and CZ collected the medical records, and analyzed and interpreted data. QA and CZ confirm the authenticity of all the raw data. LW was a major contributor in writing the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by Ethics Committee of First Affiliated Hospital of Xi'an Jiaotong University (approval no. 2022-291) and was performed in accordance with the Declaration of Helsinki. The study protocol and data collection instruments were submitted and approved by the Data Protection Commission of Xi'an Jiaotong University. All patients provided their written informed consent prior to inclusion in the study.s

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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