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RESEARCH ARTICLE

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The diagnostic and prognostic value of growth differentiation factor-15 in systemic lupus erythematosus-associated pulmonary arterial hypertension

Junyan Qian[1] | **Yufang Ding**[1,2] | **Xiaoxi Yang**[1] | **Qian Wang**[1] | **Jiuliang Zhao**[1] | **Yongtai Liu**[3] | **Zhuang Tian**[3] | **Yanhong Wang**[4] | **Mengtao Li**[1] | **Xiaofeng Zeng**[1]

[1]Department of Rheumatology and Clinical Immunology, State Key Laboratory of Complex Severe and Rare Diseases, Key Laboratory of Rheumatology and Clinical Immunology, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Peking Union Medical College Hospital (PUMCH), Peking Union Medical College & Chinese Academy of Medical Sciences, Ministry of Education, Beijing, China

[2]Class 2017, China Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[3]Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China

[4]Department of Epidemiology and Bio-Statistics, Institute of Basic Medical Sciences, China Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Correspondence
Mengtao Li and Xiaofeng Zeng, Department of Rheumatology, Peking Union Medical College Hospital, No. 1 Shuaifuyuan, Wangfujing Ave, Beijing 100730, China.
Email: mengtao.li@cstar.org.cn and zengxfpumc@163.com

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Abstract

Growth-differentiation factor (GDF)-15 is a member of transforming growth factor-β-related cytokine and may respond to right ventricular overload. The objective of this article was to assess the diagnosis and prognostic value of GDF-15 in systemic lupus erythematosus-associated pulmonary arterial hypertension (SLE-PAH). Serum samples were obtained from 65 patients with SLE-PAH, 51 sex and age matched patients of SLE without PAH (SLE-non-PAH), and 32 healthy controls. Serum GDF-15 level was detected by enzyme-linked immunosorbent assay and the optimal cut-off point was determined by receiver operating characteristic curve. The primary end-point was death from any cause and the secondary end-point was target goal achievement (TGA). Cox regression analyses and Kaplan–Meier method were performed to identify the prognostic value of GDF-15. Serum GDF-15 levels were significantly higher in SLE-PAH patients (1112.14 ± 781.80 pg/mL) than SLE-non-PAH patients (810 ± 408 pg/mL) and healthy controls (442 ± 139 pg/mL) at baseline. The optimal cut-off value of GDF-15 in the diagnosis of SLE-PAH was 733 pg/mL (AUC = 0.84). In patients with SLE-PAH, GDF-15 level was associated

Junyan Qian and Yufang Ding contributed equally to this work.

with 6 min walking distance ($\rho = -0.385$, $p = 0.017$) and higher serum N terminal-pro brain natriuretic peptide (NT-proBNP) ($\rho = 0.605$, $p < 0.001$). Patients with GDF-15 > 733 pg/mL were more likely to death (adjusted hazard ratio [HR] = 4.01, 95% confidence intervals [CI]: 1.23–6.27, $p = 0.041$) and less likely to achieve treatment goal (adjusted HR = 0.57, 95% CI: 0.23–0.79, $p = 0.028$). In addition, patients with simultaneous elevation of GDF-15 and NT-proBNP showed lower proportion of TGA ($p = 0.046$). In conclusion, GDF-15 is a new and promising biomarker of development and prognosis in SLE-PAH. The combination of GDF-15 and NT-proBNP may provide more accurate prognostic information.

KEYWORDS

GDF-15, prognostic factor, pulmonary arterial hypertension, risk factor, systemic lupus erythematosus

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by pulmonary vascular remodeling and progressive elevation of pulmonary vascular resistance (PVR).[1] Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with complicated clinical manifestations[2] PAH is a severe vascular complication of approximately 3.8% of SLE patients in China and has been identified as the third leading cause of mortality in SLE patients.[3] In a multicenter prospective study in China, the 1, 3, and 5-year survival rates of SLE-associated pulmonary arterial hypertension (SLE-PAH) patients were 92.1%, 84.8%, and 72.9%, respectively.[4] SLE affects mostly females (female: male ratio 9:1[5]) and 99.4% SLE-PAH are woman.[4] According to 2022 European Society of Cardiology/the European Respiratory Society (ESC/ERS) guideline,[6] connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) belongs to group I pulmonary hypertension. In addition to clinical and hemodynamic parameters, biomarkers are increasingly used in SLE-PAH as tools to identify PAH in SLE patients and to assess the prognosis.[4] The most predominantly used biomarkers are brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP).[7] Circulating levels of these biomarkers are correlated with disease severity and were included in the risk stratification of PAH.[8] However, SLE-PAH is a disease in which heterogeneity introduces major challenges in early diagnosis and risk stratification. Thus, the imperative need for novel biomarkers that may be effective in the early diagnosis and management of SLE-PAH patients remains.

Growth differentiation factor (GDF)-15 is a member of the transforming growth factor-β cytokine superfamily and was a marker of multiple cellular stress pathways in the heart tissue.[9] Previous studies found that GDF-15 is induced significantly in response to cardiac pressure overload, oxidative stress, and inflammation. What is more, GDF-15 affects the proliferation and migration of pulmonary endothelial cells, and thus may be vital in the pathogenesis of PAH.[10,11] Therefore, GDF-15 could be an ideal diagnosis and prognostic biomarker of PAH.[12] In idiopathic pulmonary arterial hypertension (IPAH), GDF-15 was correlated with PVR and pulmonary arterial wedge pressure (PAWP).[13] Similar in systemic sclerosis-associated PAH (SSc-PAH), GDF-15 was found abundantly expressed in SSc-PAH and was correlated with pulmonary artery systolic pressure (PASP).[14] However, it remains uncertain if GDF-15 may serve as a marker for SLE-PAH. We hypothesized (1) that patients with SLE-PAH would have elevated serum levels of GDF-15 protein compared with SLE patients without PAH and (2) that GDF-15 may provide prognostic information in SLE-PAH patients.

METHODS

Patients recruitment

In this study, we consecutively collected patients with SLE-PAH (SLE-PAH group, $n = 65$), SLE patients without PAH (SLE-non-PAH group, $n = 51$) with matched age, gender, SLE duration, and SLEDAI, and healthy controls (HC group, $n = 32$) with matched age and sex. All patients were enrolled between February 2006 and December 2016 from Peking Union Medical College Hospital (PUMCH). All 116 SLE patients fulfilled the revised American College of Rheumatology classification

criteria for SLE (1997)[15] or 2012 classification criteria of the Systemic Lupus International Collaborating Centers group.[16] SLE-PAH patients were diagnosed based on results of right-sided heart catheterization (RHC), with a mean pulmonary artery pressure (mPAP) of ≥25 mmHg, a PAWP of ≤15 mmHg, and PVR of >3 Wood units.[17] All RHCs were performed at PUMCH with a standard technique. Patients with left-sided heart insufficiency, interstitial lung disease, or pulmonary thromboembolism were excluded. The pulmonary thromboembolism was tested by ventilation/perfusion scintigraphy or computed tomographic pulmonary angiography in our study. Patients with overlapping CTD were also excluded. All patients in the SLE-non-PAH group had a PASP of ≤36 mmHg determined by echocardiography (ECHO). Healthy subjects (HC group) were self-identified as having neither PAH nor CTD. The protocol was approved by the Medical Ethics Committee of Peking Union Medical College Hospital. Written informed consents were obtained from all patients.

Data collection

The time of baseline was defined as the time of SLE-PAH diagnosis confirmed by RHC. Data collected at baseline included age, sex, organ involvements, SLE disease activity index (SLEDAI), World Health Organization functional class (WHO Fc), levels of serum BNP and NT-proBNP, anti-ribonucleoprotein (anti-RNP) antibody status, and antiphospholipid antibodies status. Exercise capacity was represented by 6-min walking distance (6MWD). RHC parameters included mPAP, PAWP, PVR, cardiac output, cardiac index (CI), right atrial pressure (RAP), and oxygen saturation of mixed venose blood (SvO_2).

Laboratory analyses

In the SLE-PAH group, clinical characteristics, medical histories, laboratory tests, and blood samples were collected within 1 month of the initial RHC. In the SLE-non-PAH group, blood samples were collected within 1 month of patients enrollment. All blood samples were immediately cooled on ice and centrifuged at −80°C. Then serum samples were collected and stored at −80°C. GDF-15 serum concentrations were measured by a GDF-15 Duoset enzyme-linked immunosorbent assay Development kit (R&D Systems) following R&D's protocol. Plates were read on a VersaMax microplate reader (Molecular Devices) at 450 nm, with a wavelength correction of 630 nm. Results were analyzed using SoftMax Pro v4.8 analysis software (MDS Analytical Technologies). The amino terminal propeptide form of NT-proBNP levels was determined by a sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostics).

Follow-up and outcome

All patients received a comprehensive evaluation every 3−6 months. Clinical records were reviewed to collect SLE-associated parameters (mainly for autoantibodies profile, complements, SLEDAI, and organ damage) and PAH-associated parameters (WHO Fc, 6MWD, serum BNP/NT-proBNP level, and ECHO). The primary end-point was death from any cause. The secondary end-point was target goal achievement (TGA) recommended by 2015 and 2022 ESC/ERS guideline.[6,17] TGA was defined as achieved when all of the following four aspects were reached. (1) Clinical symptoms: no signs of right heart failure, syncope, or progression of symptoms; (2) WHO Fc I or II or 6MWD > 440 m or Peak VO_2 > 65% pred in cardiopulmonary exercise testing; (3) serology: BNP < 50 pg/L or NT-proBNP < 300 pg/L; and (4) cardiac imaging: right atrial area <18cm,^{2} TAPSE/sPA*p* >0.32 mm/mmHg, and no pericardial effusion according to ECHO. Hemodynamic parameters (RAP < 8 mmHg, CI ≥ 2.5 L/min/m,^{2} SvO_2 > 65%, SVI > 38 mL/m^2) were not included in the criteria of TGA in our study due to socioeconomic reasons.

Statistical analyses

Data are presented as absolute numbers, frequency (for categorical variables), or median ± standard deviations (for continuous variables). χ^2 tests were performed to compare proportions and student *t*-tests were performed to compare continuous variables. Relations between GDF-15 and clinical characteristics were assessed by Spearman's rank correlation coefficients, since the concentration of GDF-15 did not accord with normal distribution. The diagnosis value of GDF-15 was first assessed by univariate logistic regression analysis. Receiver operating characteristic (ROC) curves were generated to further examine the usefulness of serum GDF-15 concentrations in discriminating SLE patients with PAH from those without PAH. The optimal cut-off point of GDF-15 was chosen based on the highest Youden index and was further verified by logistic regression analysis. Univariable and multivariate Cox

regression analyses were performed to identify predictors of death and TGA during follow-up. Cumulative probabilities of survival and TGA were calculated by the Kaplan–Meier method with comparisons performed using the log-rank test for trends between different baseline GDF-15 levels, alone or in combination with NT-proBNP. The results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). All tests of significance were two-sided and a p value of <0.05 was considered to be statistically significant. Statistical analysis was performed by using SPSS 24.0 (IBM) and R Statistical Software, version 3.6.1 (R Foundation for Statistical Computing).

RESULTS

Patients enrollment

In our study, 150 subjects were enrolled, including 65 SLE-PAH patients, 51 SLE-non-PAH patients, and 32 HCs. In the 65 enrolled SLE-PAH patients, the average age was 32.6 ± 7.1 years old, with a mean SLE duration of 8.0 ± 6.9 years and a SLEDAI score of 3.1 ± 2.4 at baseline. The mean time to follow-up was 34.0 ± 10.7 months, with a maximum follow-up of 86 months and a minimum of 2.3 months. During follow-up, 7 (10.8%) SLE-PAH patients died of all-cause and 29 (45.6%) SLE-PAH patients achieved TGA.

GDF-15 levels and diagnosis of SLE-PAH

The GDF-15 levels of SLE-PAH patients ranged from 219 to 4617 pg/mL, with an average value of 1112.14 ± 781.80 pg/mL. As shown in Figure 1, the level of GDF-15 was significantly higher in SLE-PAH patients than that in SLE patients without PAH (810 ± 408 pg/mL) and HCs (442 ± 139 pg/mL) ($p < 0.05$, Spearman's test). Univariate logistic regression analysis confirmed the association between GDF-15 level and the development of SLE-PAH (OR = 2.29, 95% CI: 2.08–2.35, $p = 0.002$). In patients with SLE, the ROC curve was generated for the diagnosis of PAH using GDF-15 serum values (Figure 2). The area under curve (AUC) was 0.84, with a p-value of <0.001. Based on the highest Youden index, 733 pg/mL was chosen as the optimal cut-off of GDF-15, with 91% sensitivity and 58.6% specificity for the diagnosis of SLE-PAH. The relation of GDF-15 serum levels ≥733 pg/mL to the diagnosis of SLE-PAH was statistically significant in univariate logistic regression (OR = 13.42, 95% CI: 5.00–35.92, $p < 0.001$).

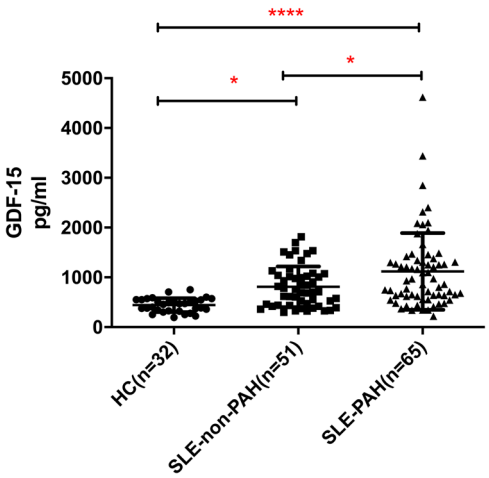

FIGURE 1 GDF-15 expression in serum. *$p < 0.05$; ***$p < 0.001$. GDF, growth-differentiation factor; HCs, healthy controls; SLE-PAH, systemic lupus erythematosus-associated pulmonary arterial hypertension.

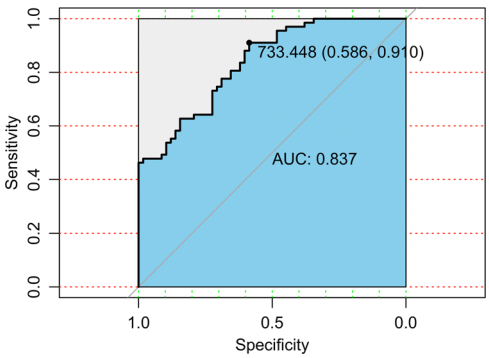

FIGURE 2 ROC curve analyse of GDF-15 in SLE-PAH diagnosis. GDF-15, growth differentiation factor-15; ROC, receiver operating characteristic; SLE-PAH, systemic lupus erythematosus-associated pulmonary arterial hypertension.

Association of GDF-15 with clinical, biochemical, and hemodynamic parameters

As shown in Table 1, elevated levels of GDF-15 (≥733 pg/L) in patients with SLE-PAH were associated with higher WHO Fc, lower 6MWD, higher PVR, lower CI, lower diffusion lung capacity for carbon monoxide (DLCO), and more elevated levels of NT-proBNP. No significant differences were observed with regard to mPAP, RAP, forced vital capacity, and total lung capacity. The relations between GDF-15 and NT-proBNP ($\rho = 0.605$, $p < 0.001$), 6MWD ($\rho = -0.385$, $p = 0.017$), PVR ($\rho = 0.137$, $p = 0.046$), CI ($\rho = -0.303$, $p = 0.019$), and DLCO ($\rho = 0.411$, $p = 0.006$) are illustrated in Figure 3.

TABLE 1 Baseline comparisons between SLE-PAH patients with high and low GDF-15 levels.

	SLE-PAH ($n = 65$)	GDF-15 < 733 pg/mL ($n = 27$)	GDF-15 ≥ 733 pg/mL ($n = 38$)	p Value
Sex (female/male)	63/2	26/1	37/1	0.733
Age (year)	32.6 ± 7.1	32.8 ± 8.0	32.5 ± 9.0	0.696
SLE duration (year)	8.0 ± 6.9	8.2 ± 6.2	7.2 ± 7.1	0.562
PAH duration (year)	1.7 ± 2.1	1.8 ± 1.9	1.6 ± 2.0	0.747
Reynolds phenomenon, *n* (%)	47 (72.4%)	21 (76.0%)	26 (68.4%)	0.350
SLEDAI	3.1 ± 2.4	2.9 ± 1.7	3.1 ± 2.1	0.132
WHO functional class *n* (%)				
I	4 (6.2%)	3 (11.1%)	1 (2.6%)	**0.037**
II	26 (40%)	15 (55.6%)	11 (28.9%)	
III	35 (53.8%)	9 (33.2%)	26 (68.4%)	
IV	0 (0)	0 (0%)	0 (0%)	
6 min walking distance (m)	419 ± 100.1	464.4 ± 109.1	377.0 ± 72.5	**0.017**
BNP (pg/L)	286 ± 314.4	304.9 ± 516.5	272.8 ± 204.8	0.493
NT-proBNP (pg/mL)	1443.3 ± 1021.1	860.7 ± 788.0	2026.0 ± 1802.5	**0.002**
Right-sided catheterization				
mPAP (mmHg)	51.2 ± 12.1	51.8 ± 10.3	50.7 ± 14.3	0.739
PVR (WU)	10.3 ± 4.2	8.5 ± 3.2	12.1 ± 5.1	**0.046**
CI (L/min × m^2)	2.7 ± 0.8	3.2 ± 1.1	2.1 ± 0.3	**0.019**
RAP (mmHg)	3.8 ± 4.0	3.7 ± 3.1	3.9 ± 4.8	0.899
Echocardiogram				
RV transverse diameter (mm)	42.0 ± 8.0	41.0 ± 6.9	44.6 ± 9.1	0.128
RV lateral and anteroposterior diameter (mm)	31.0 ± 6.8	31.8 ± 6.9	30.1 ± 6.7	0.391
Pulmonary function test				
FVC/Pred (%)	76.6 ± 14.3	78.9 ± 15.5	74.3 ± 13.6	0.321
TLC/Pred (%)	88.2 ± 10.2	90.3 ± 12.6	86.9 ± 9.9	0.373
DLCO/Pred (%)	66.1 ± 13.8	73.3 ± 14.3	58.8 ± 12.6	**0.006**

Note: Data are presented as mean ± SD or *n* (%), unless otherwise stated. $p < 0.05$ were shown in bold.

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; DLCO, diffusion lung capacity for carbon monoxide; FVC, forced vital capacity; GDF-15, growth differentiation factor-15; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-BNP; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SLEDAI, SLE disease activity index; SLE-PAH, systemic lupus erythematosus-associated pulmonary arterial hypertension; TLC, total lung capacity.

The prognostic utility of GDF-15 levels in SLE-PAH

Besides diagnosis of SLE-PAH, elevated serum GDF-15 levels were also associated with prognosis. In univariate Cox regression analysis, we confirmed the prognostic value of GDF-15 and NT-proBNP. The diagnostically relevant value for NT-proBNP of 1350 pg/mL was derived from the ROC curve (Supporting Information: Figure S1). As shown in Table 2, GDF-15 ≥ 733 pg/L (HR = 4.96, 95% CI: 2.88−7.99, $p = 0.039$) was risk factor of death. Both GDF-15 ≥ 733 pg/L (HR = 0.48, 95% CI: 0.23−0.98, $p = 0.047$) and NT-proBNP ≥ 1350 pg/mL (HR = 0.41, 95% CI: 0.19−0.88, $p = 0.034$) were associated with TGA. In the multivariate Cox regression analysis, we considered 6MWD < 380 m, and WHO FC III or IV as potential confounders (Table 2). After accounting for potential confounders, GDF-15 ≥ 733 pg/L remained

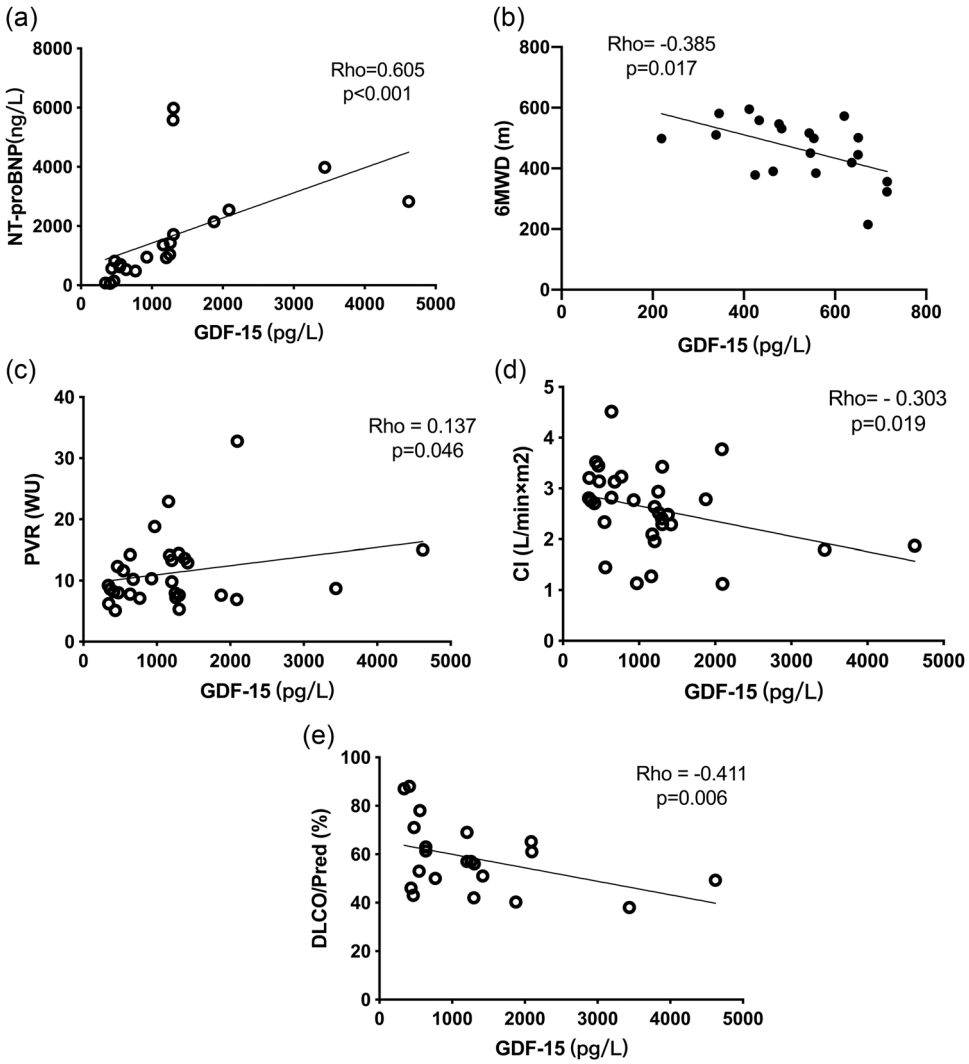

FIGURE 3 (a) The correlations between GDF-15 and NT-proBNP. (b) The correlations between GDF-15 and 6MWD. (c) The correlations between GDF-15 and PVR. (d) The correlations between GDF-15 and CI. (e) The correlations between GDF-15 and DLCO. CI, cardiac index; DLCO, diffusion lung capacity for carbon monoxide; GDF, growth-differentiation factor; NT-proBNP, N-terminal pro-BNP; PVR, pulmonary vascular resistance; 6MWD, 6 min walking distance.

independently associated with death (adjusted HR = 4.01, 95% CI: 1.23−6.27, $p = 0.041$) and TGA (adjusted HR = 0.57, 95% CI: 0.23−0.79, $p = 0.028$). Similarly, NT-proBNP ≥1350 pg/mL remained negative correlated with TGA (adjusted HR = 0.68, 95% CI: 0.12−0.91, $p = 0.045$).

As shown in Figure 4a, there was a significant difference between the Kaplan−Meier survival curve of SLE-PAH patients with GDF-15 ≥ 733 pg/mL and with GDF-15 < 733 pg/mL. In patients with GDF-15 ≥ 733 pg/mL, the survival probabilities after 1, 3, and 5 years of follow-up were 94.7% (36/38), 89.5% (34/38), and 84.2% (32/38), respectively. While in patients with GDF-15 < 733 pg/mL, the survival probabilities after 1, 3, and 5 years of follow-up were 100%, 96.3% (26/27), and 96.3% (26/27), respectively. The secondary endpoint of our study was TGA. As shown in Figure 4b, patients with GDF-15 < 733 pg/mL were more likely to achieve TGA. In patients with GDF-15 ≥ 733 pg/mL, the proportion of TGA after 1, 3, and 5 years of follow-up were 10.53% (4/38), 26.3% (10/38), and 26.3% (10/38), respectively. While in patients with GDF-15 < 733 pg/mL, the proportion of TGA after 1, 3, and 5 years of follow-up were 44.4% (12/27), 55.6% (15/27), and 66.7% (18/27), respectively.

The combination of GDF-15 and NT-proBNP in predicting death and TGA

ROC curve analyses further illustrated that GDF-15 is a novel indicator of predicting TGA in SLE-PAH. The best GDF-15 cut-off level for predicting adverse TGA was 896 pg/L (sensitivity = 94.3%, specificity = 70%). As

TABLE 2 Univariable and multivariable analysis of associations between GDF-15 with death and TGA.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***p* Value**	**Adjusted HR (95% CI)**	***p* Value**
Death prediction				
GDF-15 ≥ 733 pg/L	4.96 (2.88−7.99)	**0.039**	4.01 (1.23−6.27)	**0.041**
NT-proBNP ≥ 1350 pg/mL	2.83 (0.46−11.22)	0.130		
6MWD < 380 m	1.37 (0.08−1.74)	0.209		
WHO FC III/IV	1.42 (0.16−3.06)	0.190		
TGA prediction				
GDF-15 ≥ 733 pg/L	0.48 (0.23−0.98)	**0.047**	0.57 (0.23−0.79)	**0.028**
NT-proBNP ≥ 1350 pg/mL	0.41 (0.19−0.88)	**0.034**	0.68 (0.12−0.91)	**0.045**
6MWD < 380 m	0.85 (0.22−2.17)	0.942		
WHO FC III/IV	0.57 (0.24−1.01)	0.447		

Note: $p < 0.05$ were shown in bold.

Abbreviations: GDF, growth-differentiation factor; HR, hazard ratio; NT-proBNP, N-terminal pro-BNP; TGA, target goal achievement; WHO FC, world health organization functional class; 6MWD, 6 min walking distance.

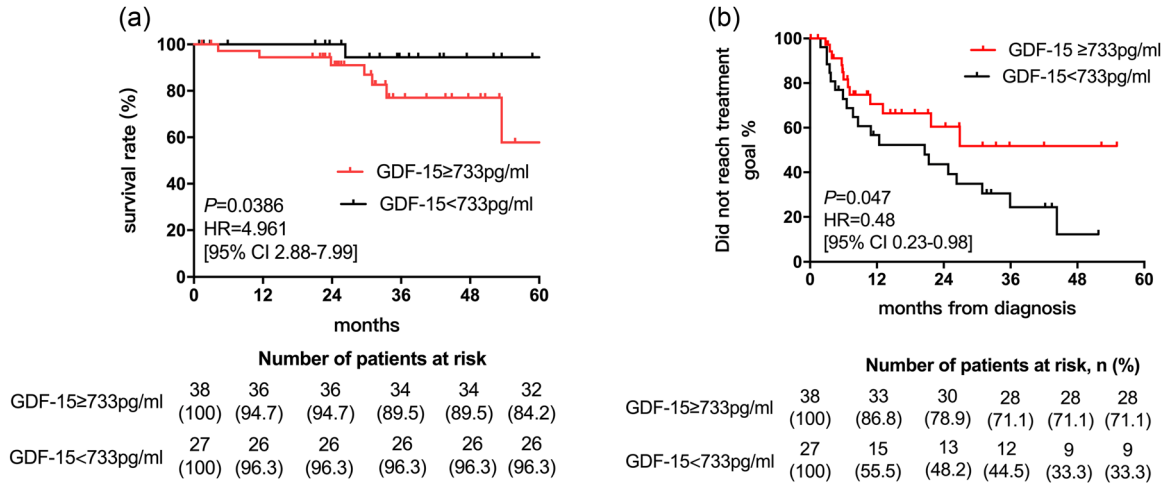

FIGURE 4 (a) Kaplan−Meier survival curve for dichotomous level of GDF-15 (733 pg/mL). (b) The proportion of fail to TGA for dichotomous level of GDF-15 (733 pg/mL). CI, confidence intervals; GDF, growth-differentiation factor; HR, hazard ratio; TGA, target goal achievement.

shown in Figure 5, GDF-15 appeared to show higher AUC in predicting TGA than pivotal hemodynamic parameters, including CI and PVR. The AUC for GDF-15 was 0.80 (95% CI: 0.51−0.92), which was higher than that of NT-proBNP (AUC = 0.72, 95% CI: 0.61−0.76), PVR (AUC = 0.69, 95% CI: 0.55−0.83), and CI (AUC = 0.61, 95% CI: 0.46−0.75).

Furthermore, the combination of GDF-15 and NT-proBNP provided more prognostic information. In our study, NT-proBNP ≥ 1350 pg/mL was associated with TGA but not survival (Supporting Information: Figure S2). As shown in Figure 6b, in patients with NT-proBNP ≥ 1350 pg/mL and GDF-15 ≥ 733 pg/L, the proportion of TGA was remarkable higher than that in patients with elevated NT-proBNP or GDF-15. No significant differences were found in survival between patients with GDF-15 < 733 pg/L and NT-proBNP < 1350 pg/mL, and other groups.

DISCUSSION

PAH is a common and severe complication of SLE.[18] Noninvasive biomarkers are needed to help identify and risk-stratify SLE-PAH patients. In our study, we confirmed GDF-15 as a useful biomarker of SLE-PAH

prognosis. ROC curve analysis revealed that GDF-15 was a potential novel biomarker in identifying PAH in SLE patients with an optimal cut-off value of 733 pg/mL. SLE-PAH with GDF-15 ≥ 733 pg/mL had a higher risk of death and lower proportion of TGA during follow-up. What is more, we identified that the combination of GDF-15 and NT-proBNP may improve the risk stratification of SLE-PAH patients. A GDF-15 ≥ 733 pg/mL with NT-proBNP ≥ 1350 pg/mL indicates the patients are at a particularly high risk of poor TGA.

Compared with SLE patients without PAH, SLE-PAH patients had elevated serum concentrations of GDF-15. Serum GDF-15 levels were significantly correlated with other indicators of PAH in SLE patients, including a significant positive correlation with estimated WHO FC, NT-proBNP, and PVR, and an inverse correlation with 6MWD, CI, and DLCO. GDF-15 is a stress-responsive member of the TGF-β cytokine superfamily. In IPAH, the association between GDF-15 and increases mPAP, decreased SvO_2, and higher levels of uric acid and NT-proBNP was confirmed by Nickel et al.[13] Similarly, the relationship between elevation of GDF-15 and PAH was also confirmed in SSc patients.[14] In SSc-PAH, GDF-15 was also correlated well with plasma levels of NT-proBNP, DLCO, and estimated right ventricular systolic pressure on ECHO. Our study confirmed these findings, and further found a correlation between GDF-15 and hemodynamic parameters, including PVR and CI, as well as 6MWD which weighed the exercise ability. The correlations found in our study indicated that GDF-15 is directly related to SLE-PAH and is a potential diagnostic marker of this sever complication of SLE. The AUC was 0.84 and GDF-15 ≥ 733 pg/mL showed 91% sensitivity and 58.6% specificity for the diagnosis of SLE-PAH. Compared with IPAH and SSc-PAH, SLE-PAH was by characterized more active immunological and inflammatory mechanisms.[19] The autoimmune mechanisms may contribute to the unique value of GDF-15 in SLE-PAH compared to the other PAH forms. The low specificity of GDF-15 needed further validation in a larger cohort.

Besides diagnosis, our study identified the potential prognostic value of GDF-15 and its possible use in risk stratification strategies. It is generally accepted that the therapeutic regimen should be determined based on the risk assessment in CTD-PAH patients.[20] In both PAH and SLE-PAH, TGA is associated with long-term

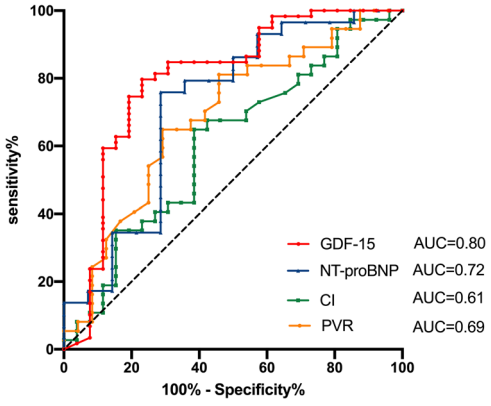

FIGURE 5 ROC curve analyses relating biomarker levels and hemodynamic parameters to 3-year proportion of TGA. CI, cardiac index; GDF-15, growth differentiation factor-15; NT-proBNP, N-terminal pro-BNP; PVR, pulmonary vascular resistance; ROC, receiver operating characteristic; TGA, target goal achievement.

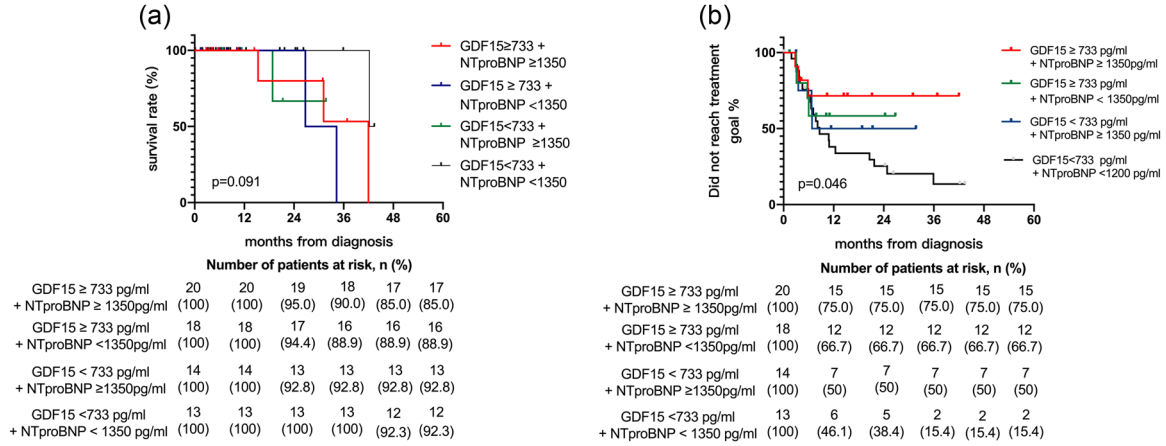

FIGURE 6 (a) Probability of survival according to baseline levels of growth differentiation factor (GDF)-15 and N-terminal pro-brain natriuretic peptide (NT-proBNP). (b) Probability of fail to TGA according to baseline levels of GDF-15 and N-terminal pro-brain natriuretic peptide (NT-proBNP). TGA, target goal achievement.

transplant-free survival.[4,21–23] Among the determinants of prognosis included in the risk stratification, hemodynamic parameters directly reflect the heart function but require an invasive procedure.[24] Thus, serum biomarkers, such as BNP/NT-proBNP, are widely used in PAH as surrogate markers of cardiac function.[25] NT-proBNP is the inactive form of Pro-BNP, which is a prohormone produced mainly by the ventricles, and is secreted by cardiomyocytes.[26] NT-proBNP has been identified as an independent predictor of survival and treatment response.[7,27] Our study, consistent with the conclusions of a meta-analysis, confirmed that NT-proBNP is related to poor TGA (adjust HR = 0.68, 95% CI: 0.12−0.91, $p = 0.045$). However, novel biomarkers are still needed to improve the risk stratification in SLE-PAH. Zelniker et al.[12] investigated GDF-15 in 65 IPAH and 21 CTD-PAH patients and found that higher GDF-15 levels were associated with a 4-year mortality risk. Besides, in group I PAH, Chang et al.[28] found that the GDF-15 level around pulmonary artery was associated with heart failure in these patients. Similarly, GDF-15 ≥ 733 pg/L was found to be associated with poor survival in our study. Moreover, to our best knowledge, the present study is the first to indicate that high a GDF-15 level was significantly related to the failure of TGA (adjust HR = 0.57, 95% CI: 0.23−0.79, $p = 0.028$). GDF-15 is a cytokine that may play a role in cell apoptosis, myocardial remodeling, cardiomyocyte hypertrophy, and myocardial fibrosis.[29–32] Previous studies have provided theoretical evidence that the expression of GDF-15 could increase in response to proinflammatory cytokines (e.g., interleukin-1β, interleukin-6, and tumor necrosis factor-α), activated B cells, oxidative stress, and acute tissue injuries.[33,34] It's well accepted that inflammation and autoimmunity play a key role in the onset and progression of CTD-PAH.[35,36] Infiltrating macrophages, autoantibodies, and interleukins have been detected in the pulmonary vessels of patients with CTD-PAH,[37,38] which may induce the production of GDF-15 in SLE-PAH. Similar to other inflammatory factors, GDF-15 may promote endothelial dysfunction and pulmonary vasculitis. In our study, GDF-15 showed a sensitivity of 94.3% and a specificity of 70% in predicting the secondary endpoint. Furthermore, we found that the combined detection of GDF-15 and NT-proBNP allows for identification of a patient subgroup with an extremely poor prognosis measured by TGA. No significant differences in death ($p = 0.091$) were found partially due to the heterogeneous risk factors of death. This result suggests that measurement of GDF-15 in patients with elevated levels of NT-proBNP may predict the prognosis more accurately. For GDF-15, a noncardiac-specific biomarker,[39] large prospective studies are needed to to document that GDF-15 can guide therapeutic decisions in the future.

In this study, we found that the combination of GDF-15 and NT-proBNP may provide more accurate prognostic information. However, our study has several limitations. First, our analysis did not clarify the exact pathological properties that enable GDF-15 to cause a poor prognosis in SLE-PAH. Second, external validation is still needed to examine the prognostic value of GDF-15. Cross-comparison between the value of GDF-15 in SLE-PAH and other forms of group I pulmonary hypertension are still needed. Besides, immunosuppressant drugs and PAH-specific drugs may affect the GDF-15 level. Blood sampling was performed within 1 week after RHC, but treatment was always initiated directly after confirmation of diagnosis. Further studies are still needed for GDF-15 to become of real incremental value in clinical practice.

CONCLUSION

In conclusion, our study confirmed GDF-15 as a new and promising biomarker of development and prognosis in patients with SLE-PAH. The combination of GDF-15 and NT-proBNP may provide more accurate prognostic information. Therefore, we suggested that the prognostic value of GDF-15 deserves further investigation.

AUTHOR CONTRIBUTIONS

Junyan Qian, Yufang Ding, Xiaoxi Yang, Mengtao Li, and Xiaofeng Zeng had the idea for and designed the study; they had full access to all data in the study and take responsibility for the integrity of the data analysis. Junyan Qian and Yufang Ding wrote the first full draft of the report. Xiaoxi Yang, Qian Wang, Jiuliang Zhao, Mengtao Li, and Xiaofeng Zeng contributed to critical revision of the report. Junyan Qian, Yufang Ding, and Yanhong Wang contributed to the statistical analysis. All authors contributed to data acquisition, data analysis, or data interpretation, and they all reviewed and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

The protocol was approved by the Medical Ethics Committee of Peking Union Medical College Hospital (Approval number, S-197). Written informed consents were obtained from all patients.

ORCID

Yufang Ding http://orcid.org/0000-0001-6426-840X

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