STUDY PROTOCOL
PULMONARY VASCULAR DISEASE

Rationale and design of the screening of pulmonary hypertension in systemic lupus erythematosus (SOPHIE) study

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ABSTRACT Current guideline-recommended screening for pulmonary hypertension in patients with systemic sclerosis has not been evaluated in systemic lupus erythematosus (SLE), which is disproportionately prevalent in Asians.

This multicentre, cross-sectional screening study aims to study the prevalence of pulmonary hypertension among SLE patients using these guidelines, and identify independent predictors and develop a prediction model for pulmonary hypertension in SLE patients.

SLE patients from participating centres will undergo an echocardiography- and biomarker-based pulmonary hypertension screening procedure as in the DETECT study. Standard right heart catheterisation will be provided to patients with intermediate or high echocardiographic probability of pulmonary hypertension. Those with low echocardiographic probability will rescreen within 1 year. The primary measure will be the diagnosis and types of pulmonary hypertension and prevalence of pulmonary hypertension in SLE patients. The secondary measures will be the predictors and prediction models for pulmonary hypertension in SLE patients. The estimated sample size is approximately 895 participants.

The results of the SOPHIE study will be an important contribution to the literature of SLE-related pulmonary hypertension and may be immediately translatable to real clinical practice. Ultimately, this study will provide the necessary evidence for establishing universal guidelines for screening of pulmonary hypertension in SLE patients.

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Introduction

Pulmonary arterial hypertension is a devastating and often life-threatening complication of connective tissue diseases. In the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL), a 55-centre longitudinal US-based registry involving 3515 patients with pulmonary arterial hypertension, connective tissue disease accounted for >50% of all patients with pulmonary arterial hypertension, in which systemic sclerosis comprised the largest connective tissue disease-related pulmonary arterial hypertension [1]. Despite advances in pharmacological therapy, the majority of patients with the condition remain asymptomatic and the diagnosis is often made late in the course of the disease when most small pulmonary arteries have been obliterated, rendering this therapy ineffective. For instance, 79% of new cases of systemic sclerosis-related pulmonary arterial hypertension in the French Pulmonary Arterial Hypertension Network between 2006 and 2009 were in New York Heart Association functional class III or IV at the time of diagnosis [2]. As such, early detection of pulmonary arterial hypertension in high-risk connective tissue disease patients is recognised as a crucial next step to further improve the outcomes of this devastating condition. In the detection of pulmonary arterial hypertension in systemic sclerosis (DETECT) study in patients with systemic sclerosis [3], an echocardiography- and biomarker-based strategy has been shown to be a sensitive and noninvasive tool to identify pulmonary arterial hypertension with minimal false negatives. To date, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension recommend routine annual screening tests using resting transthoracic echocardiography, diffusion capacity of the lung for carbon monoxide and biomarkers to detect pulmonary arterial hypertension in asymptomatic systemic sclerosis patients [4].

In a stark contrast to Caucasian countries, SLE is the more common connective tissue disease than systemic sclerosis in the Asia-Pacific region, with a reported incidence ranging from 0.9 to 3.1 per 100 000 population per year and a prevalence ranging from 4.3 to 45.3 per 100 000 population, 2–3-fold more prevalent than in the Caucasian population [5]. In a recent study involving a consecutive cohort of 190 patients with connective tissue disease-related pulmonary arterial hypertension between 2006 and 2014 from China, in contrast to the US-based REVEAL registry [1], SLE instead of systemic sclerosis comprised the largest proportion of all connective tissue disease-related pulmonary arterial hypertension (58.4%), whereas systemic sclerosis accounted for only 26.3% [6]. Unlike systemic sclerosis, international guidelines [4] and expert consensus [7] do not recommend routine screening for pulmonary arterial hypertension in asymptomatic SLE patients. One of the major reasons is the wide variation of the reported prevalence of pulmonary arterial hypertension in SLE patients [8–23], ranging from 0.5% to 17.5% (table 1). This is at least partly related to the heterogeneity in study design, definition of pulmonary hypertension, and, more importantly, the infrequent use of standard right heart catheterisation to confirm and classify pulmonary hypertension as in the DETECT study for systemic sclerosis. This may adversely affect the positive and negative predictive values, and thereby the cost-effectiveness of the screening procedure [3]. Equally importantly, these studies are also limited by the small sample size, typically less than 1000 participants [24–28], hampering the prospect to identify predictors of pulmonary arterial hypertension [29] as well as to develop a prediction model for the occurrence of pulmonary arterial hypertension. Furthermore, as only a few studies originated from Asian SLE cohorts [9, 13, 18, 22], the generalisability to Asian SLE patients remains questionable.

The screening of pulmonary hypertension in SLE (SOPHIE) study is a cross-sectional screening study to apply the current ESC/ERS guideline-recommended pulmonary arterial hypertension screening algorithm

TABLE 1 Reported prevalence of pulmonary hypertension in systemic lupus erythematosus

First author [ref.]	Year	Methodology	Patients n	Prevalence %
Perez [15]	1981	Right heart catheterisation	43	9.3
Quismorio [17]	1984	Right heart catheterisation	400	0.5
Simonson [19]	1989	Echocardiographically derived PAP >30 mmHg	36	14.0
Asherson [8]	1990	Right heart catheterisation	500	5.0
Winslow [21]	1995	Echocardiographically derived PAP >30 mmHg	36	14.0
Li [13]	1999	Echocardiography and autopsy	419	4.0
Shen [18]	1999	Echocardiographically derived PAP >30 mmHg	84	11.0
Pan [14]	2000	Echocardiographically derived PAP >30 mmHg	786	5.8
Tanaka [20]	2002	Echocardiographically derived PAP >40 mmHg	194	6.2
Gonzalez-Lopez [23]	2004	Echocardiographically derived PAP >30 mmHg	204	16.0
Johnson [12]	2004	Echocardiographically derived PAP >40 mmHg	129	14.0
Chung [9]	2006	Echocardiographically derived PAP >45 mmHg	181	11.0
Farzaneh-Far [10]	2006	Echocardiographically derived PAP >35 mmHg	200	17.5
Prabu [16]	2009	Echocardiographically derived PAP >30 mmHg	283	4.2
Li [22]	2014	Echocardiographically derived PAP >40 mmHg	1934	3.8
Ghofraniha [11]	2017	Echocardiographically derived PAP >40 mmHg	50	10.0

PAP: pulmonary arterial pressure.

for systemic sclerosis to a large cohort of unselected Chinese SLE patients in Hong Kong [4]. The study objectives include: 1) to describe the prevalence of pulmonary arterial hypertension among Chinese SLE patients using the current ESC/ERS guideline-recommended screening algorithm for pulmonary arterial hypertension in systemic sclerosis, 2) to identify independent predictors of pulmonary arterial hypertension in Chinese SLE patients and 3) to develop a prediction model for pulmonary arterial hypertension in Chinese SLE patients.

Material and methods

Participating centres

The study will be conducted on a multicentre basis in Asia. Participating centres must have a specialised rheumatology clinic with more than 200 SLE patients actively followed up, in which >80% patients consent to participate in the study. We expect seven to 10 centres from the Asia-Pacific region.

Patients and patient recruitment strategy

Chinese patients fulfilling the revised American College of Rheumatology (ACR) classification criteria for SLE [30] or 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [31] from the lupus clinics in participating hospitals are eligible for the study. In addition, patients must be aged ⩾18 years at enrolment and voluntarily agree to participate by providing written informed consent. Patients with SLE followed up in the participating hospitals will be identified *via* the computerised database of the clinical management system and will be contacted by a research nurse from the participating hospitals. The design and objectives of the study will then be discussed with the research nurse. An invitation information leaflet detailing the study will be provided to the candidate patients at the same time. Patients who fail or refuse to provide written informed consent will be excluded. Table 2 summarises the five items included in the study screening procedure. According to the ESC/ERS guidelines [4], standard right heart catheterisation will be provided to patients with intermediate or high echocardiographic probability of pulmonary hypertension. For those with low echocardiographic

TABLE 2 Screening procedure for pulmonary hypertension

1) Demographic data, data pertinent to systemic lupus erythematosus and other cardiovascular risk factors/conditions
2) Standard 12-lead ECG
3) Nail-fold video capillaroscopy
4) Plasma concentration brain natriuretic peptide and other biomarkers
5) 6-min walk distance
6) Echocardiography

probability of pulmonary hypertension, the screening procedure will be repeated within 1 year to ensure the true negativity (figure 1).

Study design

SOPHIE is a multicentre, cross-sectional screening study. The study is registered with ClinicalTrials.gov (registration number NCT03446339). The study protocol has been approved by the Institutional Review Board of The University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong. Approvals from other participating hospitals will be obtained subsequently. Written consent will be obtained from each participant, and the study will be performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

Demographic data collection

Demographic data and ACR SLE criteria, date of SLE diagnosis, immunological abnormalities, SLEDAI-2K (SLE disease activity index-2K) score (supplementary appendix S1) and SLICC/ACR damage index (supplementary appendix S2) will be collected. Past and present treatment modalities for SLE together with the corresponding duration will also be recorded. In addition, cardiovascular risk factors, history of other cardiovascular disease and investigation results within 3 months, including serum urea, serum creatinine, estimated glomerular filtration rate and diffusion capacity of the lung for carbon monoxide, will also be recorded. Table 3 summarises the demographic data and data pertinent to SLE and other cardiovascular risk factors and/or conditions to be collected.

Nail-fold video capillaroscopy

Prior studies have shown that microvascular abnormalities detected by nail-fold video capillaroscopy appear to be related to the disease severity and the presence of specific autoantibodies in the serum of SLE patients [32]. However, little is known about the relationship between these abnormalities and pulmonary vasculature damage. The nail-fold of the second, third, fourth and fifth fingers of both hands in each patient will be examined using an optical probe video capillaroscope equipped with a ×200 magnification contact lens and connected to image analysis software (Videocap; DS MediGroup, Milan, Italy). Patients will be inside the examination room for a minimum of 15 min before the nail-fold examination, where the temperature is kept at 21–25°C. The pattern of microangiopathy will then be classified as "early", "active" and "late", as previously reported in systemic sclerosis [33].

Echocardiographic examination

Detailed quantitative transthoracic echocardiography examination including two-dimensional, M-mode and Doppler flow studies will be performed in all patients. Standard two-dimensional and M-mode measurements will be performed according to the recommendations of the American Society of Echocardiography [34]. Valvular regurgitation will be classified as "mild", "moderate" or "severe" using a

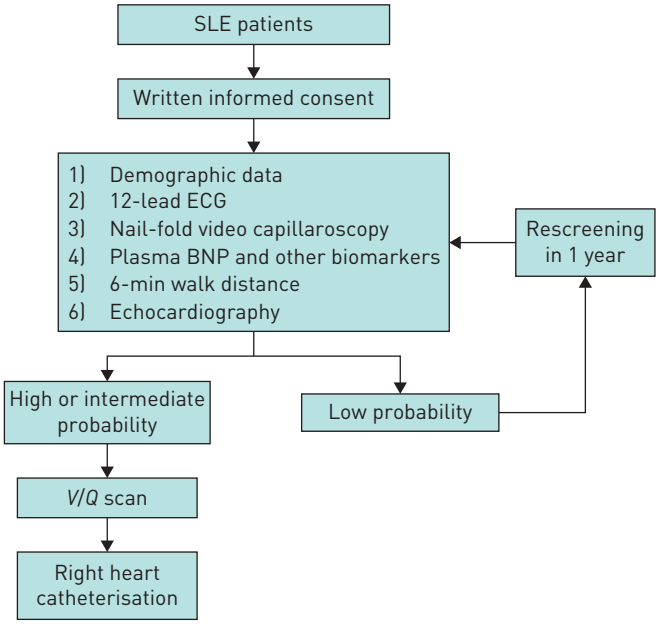

FIGURE 1 Study flow. SLE: systemic lupus erythematosus; BNP: brain natriuretic peptide; *V/Q*: ventilation/perfusion.

TABLE 3 Demographic data and data pertinent to systemic lupus erythematosus and cardiovascular diseases

Demographic	Age
	Sex
SLE	Age of diagnosis and disease duration
	Raynaud's phenomenon
	Telangiectasia
	System involvements: pleuritis, pericarditis and interstitial lung disease
	Immunological abnormalities: anti-RNP antibodies, anti-SSA/Ro antibodies and anticardiolipin antibodies
	SLEDAI-2K (supplementary appendix S1)
	Nail-fold video capillaroscopy: microangiopathy ("early", "active" and "late")
	Present and past treatment modalities and the corresponding duration for SLE
Cardiovascular data	
Risk factors	Hypertension, diabetes mellitus and hyperlipidaemia
Diseases	Coronary artery disease, peripheral artery disease, stroke, myocardial infarction, heart failure, atrial fibrillation and other conduction abnormalities
Renal function	Serum urea, serum creatinine and estimated glomerular filtration rate
Lung function test	Diffusion capacity of the lung for carbon monoxide

SLE: systemic lupus erythematosus; RNP: ribonucleoprotein; SSA: Sjögren's syndrome A; SLEDAI-2K: SLE disease activity index-2K score.

semiquantitative method [35]. A standard Doppler echocardiographic method will be used to estimate cardiac output [36]. For the calculation of cardiac output, an average of five consecutive ventricular systoles during sinus rhythm or an average of 13 beats in the case of atrial fibrillation will be obtained [37]. Simultaneous blood pressure measurements will be made with a calibrated noninvasive semiautomatic device (Dinamap 1846XT; Critikon, Tampa, FL, USA) during the determination of cardiac output. Total vascular resistance (TVR) will be calculated as:

$$\text{TVR dyn}\cdot\text{s}\cdot\text{cm}^{-5} = 80\times\frac{\text{Mean arterial blood pressure mmHg}}{\text{Cardiac output L}\cdot\text{min}^{-1}}$$

For the right heart, specific transthoracic echocardiographic measurements will be performed based on the guidelines for the echocardiographic assessment of the right heart in adults from the American Society of Echocardiography, which is endorsed by the European Association of Echocardiography [38]. Specifically, right atrial dimensions will be assessed using right atrial area (normal <18 cm^2), right atrial length (normal <53 mm) and right atrial diameter (normal <44 mm). Right ventricular dimensions will be estimated at the base (normal <42 mm) and at the mid level (normal <35 mm) as well as the longitudinal dimension (normal <86 mm) at end-diastole from a right ventricular-focused apical four-chamber view with images demonstrating the maximum diameter of the right ventricle without foreshortening (figure 2a). Additional right ventricular dimensions at the right ventricular outflow tract (RVOT) will be measured: 1) proximal RVOT diameter at the left parasternal long axis view for the proximal portion of the RVOT (normal <33 mm) and 2) distal RVOT diameter at the left parasternal short axis view demonstrating RVOT at the level of the pulmonic valve (normal <27 mm). Right ventricular wall thickness will be measured at the left parasternal view in diastole (normal <5 mm). In addition, right ventricular systolic function will be assessed using tricuspid annular plane systolic excursion and right ventricular fractional area change (FAC) (figure 2b and c) [1]:

$$\text{Right ventricular FAC }\% = 100\times\frac{\text{Right ventricular end-diastolic area} - \text{Right ventricular end-systolic area}}{\text{Right ventricular end-diastolic area}}$$

Right ventricular systolic pressure will be determined using continuous-wave Doppler echocardiography. Additional parameters for estimation of the right atrium include 1) inferior vena cava diameter and 2) Caval index, which measures the respiratory collapse of the inferior vena cava [39, 40]. Additional echocardiographic signs of pulmonary hypertension include 1) dilated right ventricle with right ventricular to left ventricular basal diameter >1.0, 2) flattening of the interventricular septum, 3) dilated pulmonary artery, 4) dilated inferior vena cava and 5) dilated right atrium. In addition, the presence and the degree of

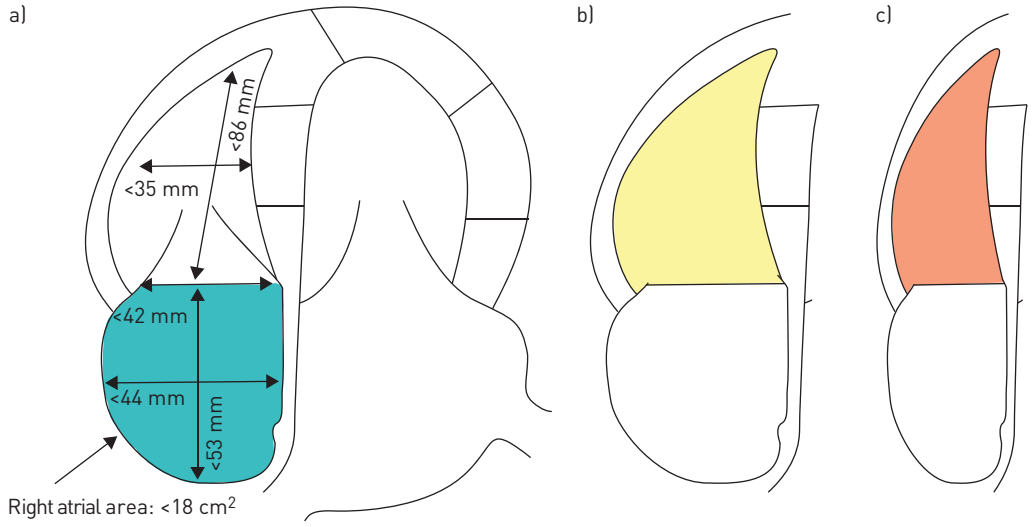

FIGURE 2 Echocardiography view. a) Apical four-chamber view showing right atrial and ventricular dimensions. b, c) Right ventricular fractional area change (see main text for calculation): b) right ventricular end-diastolic area (yellow) and c) right ventricular end-systolic area (red).

pericardial effusion as well as the possible aetiological causes will be recorded. The echocardiographic probability of pulmonary hypertension will be classified into "low", "intermediate" and "high" according to the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension (table 4) [4].

Right heart catheterisation

According to the ESC/ERS guidelines [4], standard right heart catheterisation will be provided to patients with intermediate or high echocardiographic probability of pulmonary hypertension. Pulmonary arterial hypertension is defined as mean pulmonary arterial pressure >25 mmHg with a pulmonary capillary wedge pressure ⩽15 mmHg and pulmonary vascular resistance >3 Wood units obtained at right heart catheterisation. Pulmonary hypertension will be further classified into five groups according to haemodynamic findings obtained from the right heart catheterisation, clinical presentation and other pathological findings accordingly [4].

Study measures

The primary measure will be the diagnosis and the types of pulmonary hypertension in Chinese SLE patients. The prevalence of pulmonary arterial hypertension among Chinese SLE patients will be determined. The secondary measures will be the predictors for the occurrence of pulmonary arterial hypertension in Chinese SLE patients.

Sample size calculation

The minimal sample size for the SOPHIE study is estimated based on 1) the prevalence of pulmonary arterial hypertension in SLE patients of 5–17.5%, 2) the sensitivity and specificity of the screening

TABLE 4 Echocardiographic probability of pulmonary hypertension according to European Society of Cardiology/European Respiratory Society guidelines [4]

Right ventricular systolic pressure mmHg	Peak tricuspid regurgitation velocity m·s^{-1}	Other echocardiographic pulmonary hypertension signs	Echocardiographic probability of pulmonary hypertension
31	2.8 or not measurable	No	Low
31	2.8 or not measurable	Yes	Intermediate
32–46	2.9–3.4	No	Intermediate
32–46	2.9–3.4	Yes	High
>46	>3.4	Not required	High

algorithm from the DETECT study of 97% and 35%, respectively, 3) the precision of estimates of sensitivity or specificity, and 4) type I error of 0.05 [41]. A minimum of 895 SLE patients will be required for a sensitivity of 97% and a precision estimate of 0.05 for the SOPHIE study. Approximately 2000 SLE patients will be recruited so that the sample size will be adequate.

Statistical analysis

Continuous variables will be expressed as mean with standard deviation. Statistical comparisons between SLE patients with and without pulmonary arterial hypertension will be performed using the t-test or Fisher's exact test, as appropriate. The hazard ratio and 95% confidence interval of each variable to predict pulmonary arterial hypertension will be determined using a multivariate Cox regression model with a p-value <0.1 for inclusion. The prognostic performance of models in predicting pulmonary arterial hypertension will be assessed using c-statistics. The c-statistic for the receiver operating characteristic curve will be calculated using Analyse-it for Excel (Analyse-it, Leeds, UK) with the Delong–Delong comparison for the c-statistic. A p-value <0.05 will be considered as significant. Calculations will be performed using SPSS version 12.0 (IBM, Armonk, NY, USA) and MedCalc version 13.1.2 (MedCalc, Ostend, Belgium).

Discussion

Despite advances in therapeutic options, the prognosis of pulmonary arterial hypertension remains poor. Early diagnosis of pulmonary arterial hypertension is associated with improved long-term survival and therefore early detection of pulmonary arterial hypertension in high-risk patients has been identified as a crucial next step to further improve the outcomes of this devastating condition. It is clear from the DETECT study in patients with systemic sclerosis that a multimodal approach using echocardiography and biomarkers is a sensitive, noninvasive tool to identify pulmonary arterial hypertension with minimal false negatives [3]. The approach is recommended for screening of pulmonary arterial hypertension in patients with systemic sclerosis [4]. Uncertainties exist about the extension of this strategy to other connective tissue diseases, which has not been systemically evaluated.

In the Asia-Pacific region, SLE is known to be more prevalent and severe in non-Caucasian populations; however, the body of evidence regarding Asian SLE has largely been extrapolated from studies on Asian minorities residing in the West. Indeed, the burden of connective tissue disease-related pulmonary arterial hypertension originated from SLE instead of systemic sclerosis. In fact, SLE comprises >50% of all connective tissue disease-related pulmonary arterial hypertension (58.4%) in Asians. Experience obtained from pulmonary arterial hypertension screening strategies in systemic sclerosis may serve as a model for Asian SLE patients. Extension of the screening strategy for pulmonary arterial hypertension in systemic sclerosis with known sensitivity and specificity [3] to SLE patients can harmonise and unify early detection and diagnostic strategies across different connective tissue diseases. The SOPHIE study will explore the application of the screening strategy for pulmonary arterial hypertension currently recommended for systemic sclerosis to SLE patients. As such, the SOPHIE study aims for a large sample size of at least 2000 SLE patients to ensure adequate power to document the true prevalence of pulmonary arterial hypertension. In addition, the central requirement of >80% recruitment of SLE patients is to ensure a relatively unselective study population to avoid selection or survival bias. An additional advantage of having a large study population is to allow identification of individual predictors of pulmonary arterial hypertension that can be used to develop prediction models, which can facilitate prioritisation of SLE patients for screening procedures. One of the major challenges of the SOPHIE study is that unlike the DETECT study for patients with systemic sclerosis mandating right heart catheterisation for all screened patients, in the SOPHIE study, right heart catheterisation will be performed only for patients with intermediate or high echocardiographic probability of pulmonary hypertension according to ESC/ERS guidelines [4]. Thereby, the false-negative rate based on the low echocardiographic probability of pulmonary hypertension may potentially underestimate the "true" false negativities as documented with right heart catheterisation.

In summary, we propose a cross-sectional screening study to apply the current guideline-recommended pulmonary arterial hypertension screening algorithm for systemic sclerosis to a large cohort of unselected Chinese SLE patients. The results of the SOPHIE study will provide the prevalence of pulmonary hypertension and the types of pulmonary hypertension in Chinese SLE patients. The study will also identify individual predictors for the occurrence of pulmonary arterial hypertension in Chinese SLE patients, followed by prediction model development. The SOPHIE study will be an important contribution to the SLE pulmonary hypertension literature as one of the first systemic screening studies using the established screening protocol in systemic sclerosis patients. Ultimately, this study will provide the necessary evidence for establishing universal guidelines for the screening of pulmonary hypertension in SLE patients.

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