

Efficient detection of pulmonary arterial hypertension using serum haptoglobin level and cardiac MRI in patients with connective tissue diseases: a pilot study

Sirs,
 Pulmonary arterial hypertension (PAH) develops more frequently in patients with connective tissue diseases (CTD) with the prevalence of up to 10% compared to other subjects. Early and efficient detection of PAH is therefore critical to improve the mortality and morbidity of those patients (1). European research group established an evidence-based algorithm to detect PAH in patients with systemic sclerosis (SSc), called the DETECT study. In this algorithm, right heart catheter (RHC) is recommended based on the total risk points calculated using the results of several non-invasive tests, such as laboratory examination, electrocardiogram, pulmonary function tests, echocardiography (2). This detection algorithm is highly sensitive to detect high-risk population of PAH, whereas its specificity is relatively low to lead some patients into unnecessary RHC (2, 3). Thus, additional non-invasive markers are required to improve the screening yield of PAH. Moreover, this detection algorithm is adapted for only SSc patients. Although SSc is the most major underlying disease of PAH, systemic lupus erythematosus (SLE), mixed connective tissue

disease (MCTD) and Sjögren's syndrome (SS) are also important as causes of PAH. Anti-U1-RNP antibodies are a major risk factor of CTD-PAH in Asian population in addition to anti-centromere antibodies (4). We previously reported that serum haptoglobin level (5) and ratio of right to left end-diastolic volume (RVEDV/LVEDV) calculated by cardiac MRI (6) were significantly correlated with mean pulmonary artery pressure (mPAP) measured by RHC. Decreased haptoglobin level would reflect subclinical haemolysis due to microangiopathy in pulmonary arterioles (5), and increased RVEDV/LVEDV on cardiac MRI would represent decompensation of bi-ventricular interplay (6), thus proposed as novel surrogate markers to detect PAH. In this study, we aimed to establish a non-invasive screening procedure to detect PAH in CTD patients using those potential markers. A single centre retrospective analysis comprised consecutive CTD patients who underwent RHC from July 2010 to October 2017 in Hokkaido University Hospital. We adapted the following risk factors of having PAH in CTD patients with reference to the previous reports (2, 4-9). Each cut-off levels were defined based on Japanese healthy population.

1. Positive anti-U1-RNP or anti-centromere antibodies,
2. Plasma BNP >18.4 pg/ml or NT-proBNP >55 pg/ml
3. Serum urate \geq 7.0 mg/dl
4. Presence of right axis deviation

5. %FVC/%DLCO >1.6 or %DLCO/ V_A <70%
6. Pulmonary artery systolic pressure estimated by echocardiography \geq 40 mmHg
7. Decreased serum haptoglobin level (<19 mg/dl)
8. Increased RVEDV/LVEDV on cardiac MRI (> 1.2)

Screening performance of these variables to detect PAH was expressed as area under ROC curve (AUC). Thirty-one patients (SSc: 14, MCTD: 9, SLE: 6, SS: 1 and dermatomyositis: 1) were enrolled. Of the patients, 18 patients had PAH. Both serum haptoglobin level ($r=-0.70$, $p<0.001$) and RVEDV/LVEDV ($r=0.60$, $p<0.001$) were significantly correlated with mPAP as previously reported (5, 6). AUC to detect PAH by five routine examinations (1)-(5) was 0.67. Area under ROC curve increased to 0.76 by adding echocardiography or to 0.74 by adding serum haptoglobin level to the routine examinations, and further increased to 0.82 with both of them. Moreover, addition of cardiac MRI increased AUC to 0.84 (Fig. 1). If the cut-off value is set as any four out of the eight risk factors, sensitivity and specificity for PAH detection were 88% and 58%, respectively. This pilot study suggested that addition of these non-invasive examinations to conventional risk factors may improve accuracy and efficiency in the detection of PAH, although further investigations are desired to validate and refine our pilot screening programme.

Five routine examinations*

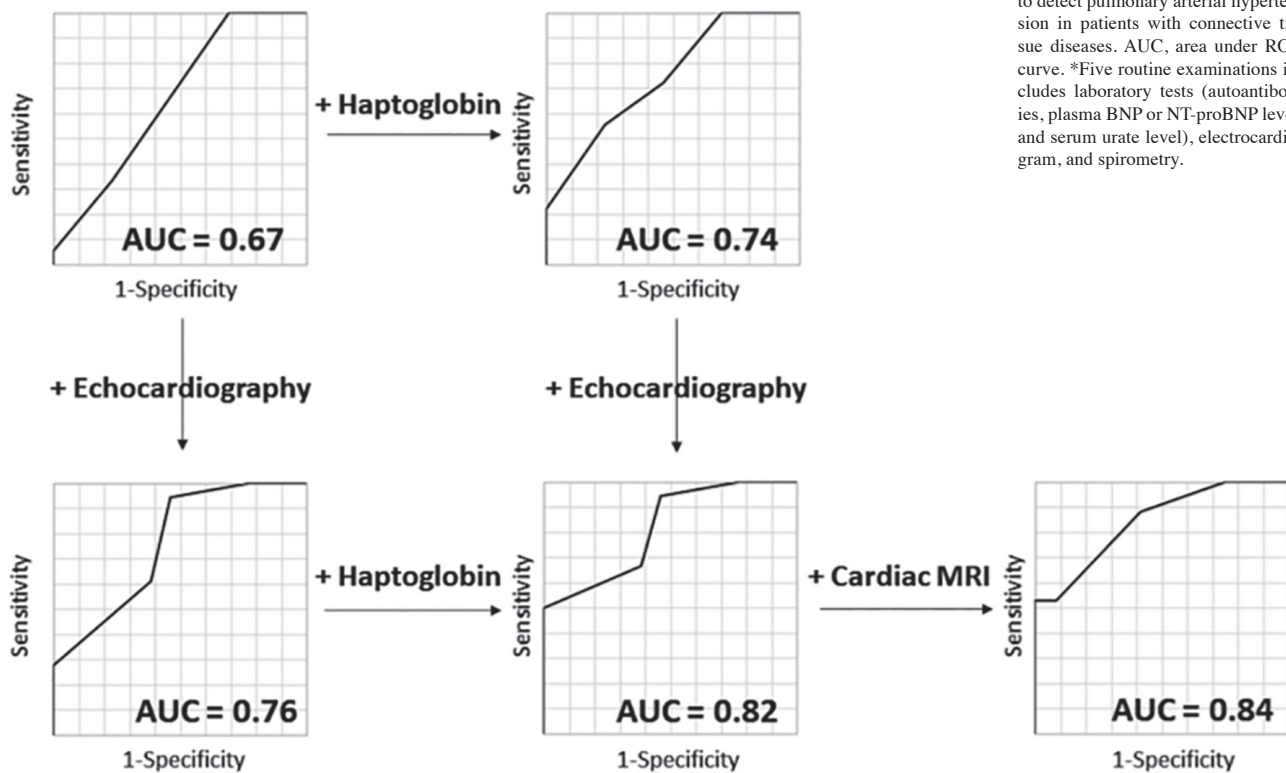


Fig. 1. A pilot screening programme to detect pulmonary arterial hypertension in patients with connective tissue diseases. AUC, area under ROC curve. *Five routine examinations includes laboratory tests (autoantibodies, plasma BNP or NT-proBNP level, and serum urate level), electrocardiogram, and spirometry.

Letters to the Editors

H. NAKAMURA, MD¹
M. KATO, MD, PhD¹
A. NOGUCHI, MD¹
H. OHIRA, MD, PhD²
I. TSUJINO, MD, PhD²
T. ATSUMI, MD, PhD¹

¹Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine,
²First Department of Medicine, Hokkaido University Hospital, Sapporo, Japan.

Please address correspondence to:
Dr Masaru Kato,
Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine, Hokkaido University, N15W7, Kita-ku, Sapporo, Japan.
E-mail: ktmassaru@med.hokudai.ac.jp

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