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Early View

Research Letter

# Prevalence of pulmonary hypertension in pulmonary sarcoidosis; the first large European prospective study

M. P. Huitema, A. L. M. Bakker, J. J. Mager, B. J. W. M. Rensing, F. Smits, R. J. Snijder, J. C. Grutters, M. C. Post

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# Title page

Prevalence of pulmonary hypertension in pulmonary sarcoidosis; the first large European prospective study

**Authors:** M.P. Huitema, MD[1]; A.L.M. Bakker, MD[1]; J.J. Mager, MD, PhD[2]; B.J.W.M. Rensing, MD[1], PhD; F. Smits[3]; R.J. Snijder, MD[2]; J.C. Grutters, MD, PhD[2,4]; M.C. Post, MD, PhD[1]

St. Antonius Hospital Nieuwegein, department of cardiology (1), pulmonology (2) and radiology (3);

University Medical Centre Utrecht, department of pulmonology (4)

**Corresponding author:**

M.P. Huitema

Telephone: +31 88 320 12 83

Fax: +31 30 603 44 20

Email: mp.huitema@antoniusziekenhuis.nl

**To the Editor,**

Sarcoidosis is a systemic disease of an unknown aetiology, in which non-caseating granulomas are formed in one or multiple organs, with pulmonary involvement in >90% of the sarcoidosis patients [1]. Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure of at least 25 mmHg by right heart catheterisation (RHC) [2] is a well-recognised complication of sarcoidosis, associated with significant increase in mortality [3,4]. Even though the first case of PH in sarcoidosis was described in 1949[5], the exact prevalence remains unclear. Only three studies have previously investigated the PH prevalence independently of suggestive symptoms and signs for PH, resulting in prevalence rates of 5.7% and 20.8% [6-8]. In patients with complaints suggestive for PH or awaiting lung transplant rates of PH up to 79% have been reported [9-11]. Unfortunately, most studies are retrospective and used an echocardiographic definition for PH (increased right ventricular systolic pressure (RVSP) of ≥40mmHg), lacking RHC as gold standard.

An European Caucasian cohort has never been studied. The PULmonary hypertension in pulmonary SARcoidosis (PULSAR) study prospectively investigates the PH prevalence in patients with pulmonary sarcoidosis referred to a Dutch tertiary sarcoidosis centre (www.trialregister.nl, registration number NTR5295). This study was funded by ZonMW.

Between August 2015 and October 2017, this cross-sectional study prospectively investigated the prevalence of PH in patients with histologically confirmed or confident clinical diagnosis of sarcoidosis. Patients with an age of 18 years or above who were newly referred to the pulmonology department of the St. Antonius hospital Nieuwegein, a tertiary centre for sarcoidosis, were asked for informed consent and underwent PH screening. Baseline data was recorded on ethnicity, Scadding stage on chest X-ray [12], pulmonary function test and chest-CT. PH screening consisted of thorough history taking, physical examination and echocardiography by the same experienced physician. Based on the ESC/ERS guideline for PH [2], patients were divided into three groups:

- Low PH probability: TRV max absent or ≤2.8m/s without secondary PH signs
- Intermediate PH probability: TRV max absent or ≤2.8m/s with secondary PH signs; or 2.9-3.4m/s without secondary PH signs
- High PH probability: TRV max 2.9-3.4m/s with secondary PH signs or TRV max >3.4m/s.

Secondary PH signs were divided in three groups in accordance to the guideline (ventricles, pulmonary artery, right atrium). It was counted as present if one or more secondary PH signs of at least two different secondary sign groups were present. All patients with intermediate or high probability were referred for RHC. Presence of PH was defined as a mean pulmonary artery pressure of at least 25mmHg. Patients with PH were discussed in a multidisciplinary PH team for the final diagnosis. Patients with a low PH probability with minor secondary signs for PH (defined as only one secondary sign or two secondary signs from the same group) were re-evaluated after one year. In case of progression patients were still referred for RHC.

As shown in the figure, 512 patients were eligible for inclusion, of whom 399 patients signed informed consent and underwent PH screening (57.9% male, mean age 49.4 ± 11.6 years). The main ethnicity was Caucasian (90.5%). Patients had a mean history of sarcoidosis for 6.0 ± 8.2 years, and 20% had Scadding stage IV sarcoidosis. Low, intermediate and high PH probability was present in

92.2, 5.5 and 1.5% respectively. High and intermediate PH probability was present in 28 patients, of whom four refused RHC. Of the low PH probability group and inconclusive echocardiograms, four patients underwent RHC based on clinical judgement, of whom none had PH. In total, 28 patients underwent RHC. In ten out of these 28 patients PH was present. One patient had a post capillary component.

As shown in the figure, patients with PH had a longer history of sarcoidosis and presented with Scadding stage IV more often. Three out of ten patients developed PH in absence of significant fibrosis.

Based on the results of echocardiography and RHC, the PH prevalence was calculated. Because a few patients with high and intermediate PH probability did not undergo RHC, the fraction PH of the patients who underwent RHC within either one of the PH probability group was multiplied by the total number of patients of the same PH probability group. The estimated PH prevalence in this cohort of sarcoidosis patients is 2.9%. This number could range from 2.5% if all of the missing RHC's in the high- and intermediate probability group would rule out PH, up to 3.5% if all would confirm PH. Of the low PH probability group, 102 patients had minor secondary signs. 98 underwent re-evaluation after one year. Only two patients showed progression of the secondary signs, in whom one PH was ruled out by RHC. The other patient had developed a severe cardiomyopathy due to cardiac sarcoidosis with a subsequent post-capillary PH.

The PULSAR study is the first large study investigating the PH prevalence in a predominantly Caucasian cohort of almost 400 consecutive sarcoidosis patients referred to a tertiary sarcoidosis centre using echocardiography and, if indicated, RHC. As a result, the PH prevalence is estimated to be around 3%. Three studies previously investigated the PH prevalence in sarcoidosis independently of symptoms or signs for PH. Handa and colleagues [6] were the first by investigating 246 consecutive

Japanese sarcoidosis patients visiting the outpatient clinic for follow up, defining PH as an RVSP of ≥40mmHg on echocardiography. They found an echocardiographic PH prevalence of 5.7%. Bourbonnais and collegues [7] prospectively evaluated 141 sarcoidosis patients with echocardiography, followed by RHC in 35 patients. PH was defined as an RVSP of 40mmHg in the absence of significant left heart dysfunction. RHC was performed in these patients, and also in patients with inconclusive echocardiography with repeatedly abnormal six-minute walk test outcomes despite optimisation of therapy. They found a PH prevalence of 14%. 88% were African American descendants, who are more likely to have sarcoidosis associated PH compared to Caucasians [13]. In a third study, Alhamad and colleagues [8][8][7] investigated 96 Arab sarcoidosis patients, defining PH as an RVSP of ≥40mmHg as measured by echocardiography. A prevalence of 20.8% was reported, with a predominance of female PH patients. The prevalence of 3% in our population is significantly lower. This might be due to a less biased and well defined study population. Furthermore, prevalence of PH might differ between ethnicities.

Although this study presents the largest cohort of sarcoidosis patients prospectively investigated for PH, there are several limitations. First, not all patients underwent the gold standard RHC due to ethical considerations. We acknowledge that echocardiography might not always rule out PH correctly in patients with low PH probability. In clinical practice, the decision to perform RHC should outweigh the potential risks. Secondly, we aimed to minimise selection bias, however some bias could not be avoided since patients with worse disease severity are more likely to be referred to a tertiary centre. At last, 62% of all patients were on immunosuppressive therapy at baseline, which might influence the haemodynamic profile at the moment of screening.

In conclusion, the PH prevalence is estimated to be around 3% in a cohort of predominantly Caucasian sarcoidosis patients referred to a Dutch tertiary centre. It can be suggested that there are ethnic differences in the prevalence of PH.

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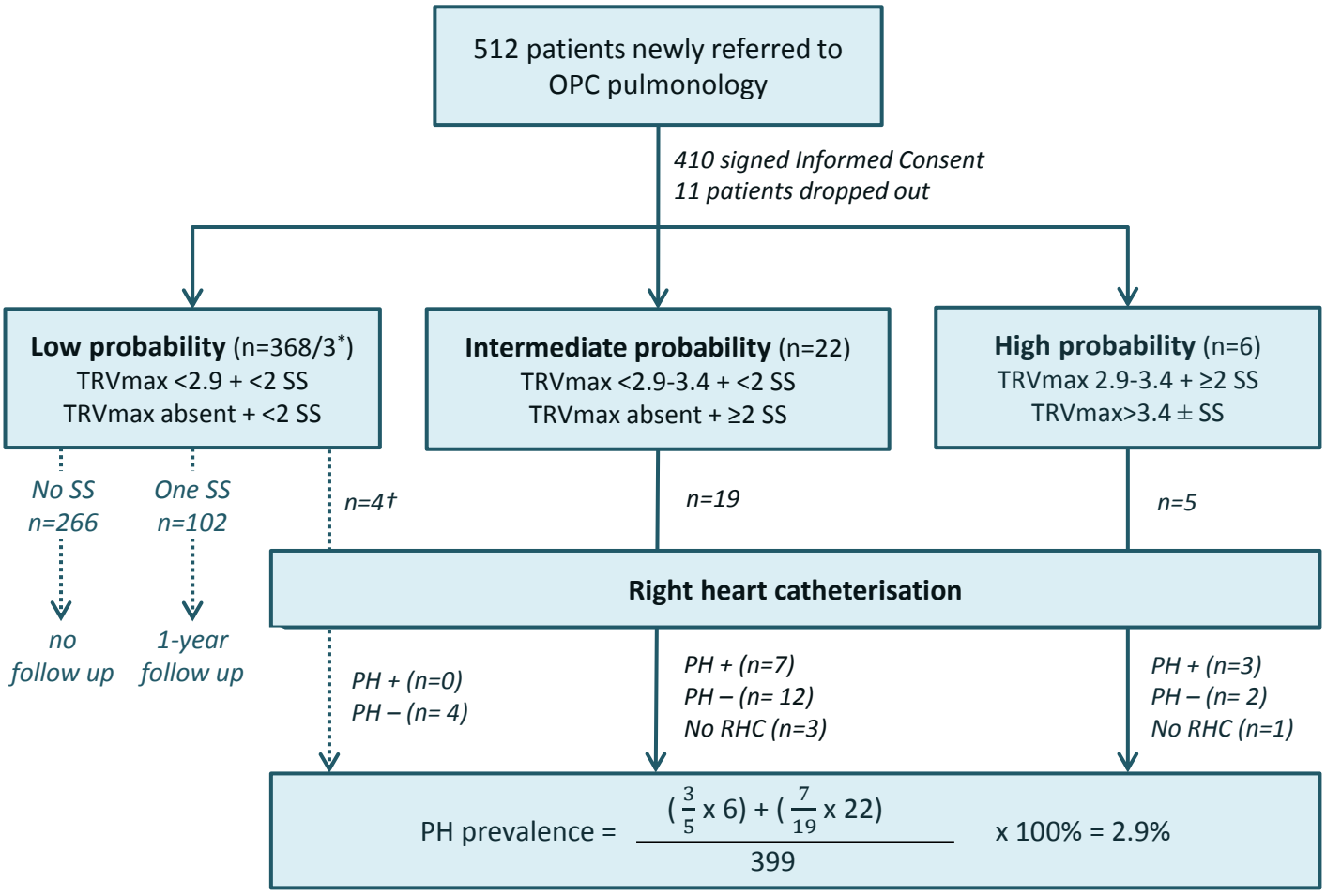
**Figure**

Figure 1: Flow-chart for PH screening, including outcomes for patients with PH present compared to PH absent. CO= cardiac output, DLCO SB= single-breath diffusing capacity of the lung; FEV1= forced expiratory volume in 1 minute; FU= follow up; FVC=forced vital capacity; OPC= outpatient clinic; PAP=pulmonary artery pressure; PCWP= pulmonary capillary wedge pressure; PVR= pulmonary vascular resistance; SS= secondary signs; TRV max = maximal tricuspid regurgitation velocity. *3 patients had an inconclusive echocardiogram. †none of the four patients with low PH probability undergoing RHC had PH.




| | PH present (n=10) | PH absent (n=18) |
|---|---|---|
| **Male** | 70.0% | 55.6% |
| **Age** (years) | 56.3±12.9 | 54.2±12.1 |
| **Caucasian** | 90.0% | 100.0% |
| | | |
| **Duration of disease** (years) | 13.2±7.4 | 5.3±10.3 |
| *0* | 0% | 13.3% |
| *I* | 10.0% | 13.0% |
| **Scadding stage** *II* | 20.0% | 3.0% |
| *III* | 0% | 33.3% |
| *IV* | 70.0% | 56.7% |
| | | |
| **FVC** *(% predicted)* | 77.7 ± 19.2 | 95.6 ± 19.0 |
| **FEV1** *(% predicted)* | 60.5 ± 15.2 | 88.1 ± 17.5 |
| **DLCO SB** *(% predicted)* | 53.2 ± 18.5 | 69.5 ±18.3 |
| | | |
| **Mean PAP** *(mmHg)* | 33.1±12.0 | 16.5±3.1 |
| **PVR** *(Wood units)* | 3.8±2.6 | 0.8±0.4 |
| **CO** *(L/min)* | 6.0±1.6 | 6.5±1.7 |
| **PCWP** *(mmHg)* | 10.2±5.0 | 9.9±3.6 |