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Original article

Clinical prediction score for identifying patients with pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis

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ABSTRACT

Background: Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension. Although diagnosis is based on pathological findings, an early diagnosis is crucial because of poor prognosis compared to other types of pulmonary hypertension. Furthermore, vasodilators may cause fatal pulmonary edema in patients with PVOD/PCH. This study aimed to identify specific characteristics for patients with PVOD/PCH to clinically diagnose PVOD/PCH.

Methods: Clinical data were obtained at baseline and were compared between 19 patients with PVOD/PCH and 55 patients with idiopathic/heritable pulmonary arterial hypertension. Receiver operating characteristic analyses were used to determine characteristics specific for patients with PVOD/PCH and a scoring system to diagnose PVOD/PCH was developed.

Results: Patients with PVOD/PCH had a smoking history and were predominantly male. Six-minute walk distance was significantly lower and oxygen desaturation was severe during the walk. Diffusion capacity of carbon monoxide was significantly low. Radiological findings included ground glass opacity on chest high-resolution computed tomography (CT) in all patients with PVOD/PCH, and thickened septal lines in 90% of the patients. Lung perfusion scintigraphy showed defect in >70% of the patients. Pulmonary edema after initiation of vasodilation therapy was frequently observed in PVOD/PCH patients. Based on these results, we identified nine important clinical characteristics and a novel scoring system was designed to clinically diagnose PVOD/PCH: male sex, smoking history, 6-minute walk distance < 285 m, minimum SpO_2 < 92% during the 6-minute walk test, %DLco < 34%, ground glass opacity and thickening of the interlobular septa in high-resolution CT, defects in the perfusion lung scan, and pulmonary edema due to vasodilators. Score ≥ 5 points had 95% sensitivity and 98% specificity to predict PVOD/PCH (area under the curve: 0.991; 95% CI: 0.976–1.000).

Conclusions: Our novel prediction rule for diagnosing PVOD/PCH may offer an early clinical diagnosis of these diseases.

Introduction

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) have been considered to be rare causes of pulmonary hypertension. However, because of advances in pulmonary hypertension treatments, more cases with PVOD/PCH have been recognized. Approximately 10% of patients who were clinically diagnosed with pulmonary arterial hypertension (PAH) were diagnosed with PVOD/PCH by histological studies [1]. Although some reports state an improvement in the prognosis of PAH [2–4], the prognoses of patients with PVOD/PCH are still poor. Patients reportedly die within 1–2 years after clinical diagnoses of pulmonary hypertension [5,6] because of the difficulty in diagnosis and lack of effective treatment for this condition. PAH-targeted therapies sometimes cause fatal pulmonary edema in patients with PVOD/PCH (Fig. 1) [7]. Establishment of diagnosis and treatment of PVOD/PCH has been a challenge in the clinical practice of pulmonary hypertension. Although the definite diagnosis is based on pathological findings [8], it is necessary to make an early clinical diagnosis considering the poor prognosis of PVOD/PCH. Despite reports regarding the clinical

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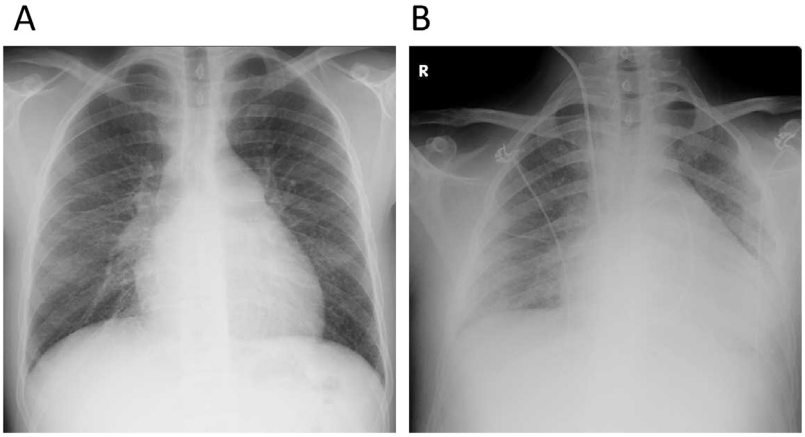

Fig. 1. Representative radiographical images of pulmonary edema induced by epoprostenol. (A) Chest X-ray of a patient with pulmonary veno-occlusive disease (PVOD) on admission shows cardiomegaly, dilatation of pulmonary arteries, and Kerley B lines. (B) Chest X-ray of a patient with PVOD after administration of epoprostenol (0.5 ng/kg/min) shows severe pulmonary edema.

characteristics of patients with PVOD/PCH [7,9], the diagnosis remains challenging. This study aimed to identify characteristics specific for PVOD/PCH and help distinguish patients with PVOD/PCH from those with idiopathic/heritable PAH (I/HPAH) based on clinical data and radiological findings.

Methods

Patient selection

Patients with PVOD/PCH and I/HPAH who underwent treatment at National Hospital Organization Okayama Medical Center (Okayama, Japan) between May 2003 and January 2015 were included in this study. A comprehensive diagnosis was made according to a standard diagnostic algorithm, including physical examination, blood chemical analysis, radiographic examination, pulmonary function test results, and right heart catheterization [10,11]. We have clinically diagnosed patients with PVOD/PCH, based on the reported characteristics of PVOD/PCH [7,9]: precapillary pulmonary hypertension confirmed by right heart catheterization, presence of radiological abnormalities characteristic of PVOD/PCH on high-resolution computed tomography (HRCT) of the chest (centrilobular ground glass opacities, thickening of interlobular septa, or lymphadenopathy), and low diffusion capacity of carbon monoxide (DLco). Furthermore, if patients demonstrate severe desaturation on exertion or develop pulmonary edema after administration of PAH-targeted therapies, we consider the possibility of PVOD/PCH is high. Pathological examination was performed on lung tissue obtained during autopsy or lung transplantation. Study protocol was approved by the Institutional Review Board (H25-RINKEN-03).

Data collection

Data were retrospectively collected from patient records and analyzed. Baseline demographic information was collected, including age, sex, smoking history, World Health Organization (WHO) functional class, plasma levels of B-type natriuretic peptide (BNP), hemodynamic parameters (mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance), 6-minute walk distance (6MWD), oxygen saturation (SpO_2), and pulmonary function test results. Results of HRCT scans and ventilation-perfusion lung scans were also evaluated. Furthermore, if treated with PAH-targeted therapies, the presence of pulmonary edema was recorded.

Statistical analysis

Continuous data are expressed as mean (standard deviation) or median (range), and categorical data are expressed as number (%). Differences between continuous and categorical variables were analyzed by unpaired *t*-test or Kruskal–Wallis test, and chi-square test, respectively. Receiver operating characteristic analyses were used to determine cut-off values for selected variables. Kaplan–Meier survival curves were used to analyze event rates for all-cause death. Patients who underwent lung transplantation were censored at the time of the operation. The follow-up period for monitoring patient survival ended on July 1, 2015. Differences between survival curves were assessed using the log-rank test. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM, Armonk, NY, USA). Statistical significance was defined as $p < 0.05$.

Results

Characteristics of patients with PVOD/PCH

There were 19 patients clinically suspected to have PVOD/PCH during this study period. In nine patients (47%) with PVOD/PCH, pathological studies confirmed the diagnosis. Two patients had PCH, while the additional seven patients had PVOD. There were 55 patients diagnosed as having I/HPAH. Diagnoses were later confirmed by pathological studies in nine patients (16%) with I/HPAH. Mean survival time of patients with PVOD/PCH was significantly worse than that of patients with I/HPAH [3.3 ± 0.5 years (95% CI, 2.3–4.2 years) vs. 22.6 ± 4.4 years (95% CI, 14.0–31.3 years), log-rank test, $p < 0.001$] (Fig. 2).

Baseline demographics were compared between PVOD/PCH and I/HPAH (Table 1). Patients with PVOD/PCH were predominantly male and the average age at diagnosis was higher than that of patients with I/HPAH. Approximately 70% of patients had a smoking history. No patients had history of exposure to organic solvents or alkylating agents. Although hemodynamic parameters were similar in both groups, patients with PVOD/PCH showed severely impaired exercise capacity. The 6MWD was significantly shorter than that of patients with I/HPAH. It is notable that patients with PVOD/PCH showed significant desaturation of oxygen during

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