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REVIEW

Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: A systematic review of the literature☆

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Summary
Rationale: There is a lack of consensus on factors that predict mortality in idiopathic pulmonary arterial hypertension (IPAH). Tests that can accurately predict prognosis are needed to guide treatment and counsel patients.
Methods: We conducted a systematic review to identify factors that prognosticate mortality in IPAH. Study design, cohort size, comparison method, measured value, and statistical significance was extracted for eight pre-selected parameters [pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), mean right atrial pressure (mRAP), cardiac output, right ventricular end diastolic pressure, functional class, 6 min walk distance (6MWD), and diffusing capacity of carbon monoxide].
Results: 107 factors have been associated with mortality in IPAH. A reproducible predictive association with mortality was demonstrated for only 10 factors: functional class (14 studies), heart rate (10 studies), 6MWD (8 studies), pericardial effusion (5 studies), mPAP (10 studies), mRAP (17 studies), cardiac index (13 studies), stroke volume index (4 studies), PVR (10 studies), mixed venous PaO_2 or saturations (4 studies). Of the 8 factors chosen for detailed

Abbreviations: 6MWD, 6 min walk distance; CO, cardiac output; CI, cardiac index; CPET, cardiopulmonary exercise; DLCO, diffusing capacity of carbon monoxide; IPAH, idiopathic pulmonary arterial hypertension; JTG, John T Granton; JRS, John R Swiston; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NIH, National Institutes of Health; NYHA, New York Heart Association; O_2, oxygen; PAH, Pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PO_2, partial pressure of oxygen; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RVEDP, right ventricular end diastolic pressure; SRJ, Sindhu R Johnson; WHO, World Health Organization.

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evaluation, there were at least half as many studies that evaluated the variable and did not find an association with mortality compared to those that did.
Conclusions: There is a large body of literature describing numerous factors that predict mortality in IPAH. Most factors have been assessed in very few studies. There are conflicting reports on the prognostic value of many factors. These discrepancies highlight the need to evaluate the literature in total when considering the utility of variables as prognostic factors in IPAH.

Contents

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a disease of unknown etiology characterized by pathological changes in the pulmonary vasculature that lead to increased pulmonary vascular resistance, elevated pulmonary arterial pressures, right ventricular dysfunction, and early death.[1] By consensus IPAH is defined by a mean pulmonary arterial pressures (mPAP) $>$ 25 mmHg at rest, a pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and an elevated pulmonary vascular resistance (PVR), with no identifiable underlying cause.[2,3]

IPAH is a devastating and progressive condition with a poor long term prognosis.[4] Given the life limiting nature of IPAH, the ability to predict disease progression and death is necessary for optimal care of these patients and timely intervention. This is particularly true given that the treatment of last resort for many patients with IPAH is lung transplantation.[5] This intervention is exquisitely sensitive to timing.[6,7] Lung transplant recipients are also subjected to increase morbidity and mortality and thus transplanting IPAH patients too early may not increase life expectancy.[8] On the other hand, referral for this procedure too late can result in death while awaiting a suitable donor thus deny patients an opportunity for an extended lifespan. Short of transplantation, the most effective intervention for IPAH remains prostacyclin.[5,9] This intervention also require careful consideration of prognosis and timing as it is administered as a continuous parenteral infusion and thus carriers a risk of life threatening complications such as sepsis and hemodynamic collapse if interrupted.[10] Furthermore, many patients are reluctant to initiate this therapy until absolutely necessary as it is cumbersome, labor intensive, and intrusive. With the recent development of oral therapies[5] (such as endothelin receptor antagonists and phosphodiesterase inhibitors) for less severe disease, prognostication has become no less important as timely initiation, escalation, combination, and abandonment of these therapies requires an ability to predict outcome.[11]

There have been significant advances in our pathophysiologic understanding of pulmonary hypertension and the diagnostic classification of this disease has been revised a number of times.[3] These advances, along with the development of new therapeutic and pharmacologic interventions have collectively changed our perspective of IPAH and the evaluation of these patients. During this time a number of new investigative techniques and markers of disease have been developed while older ones have been advanced, refined, and reevaluated.

Despite the growing number of studies evaluating prognosis and prognostic factors for mortality in IPAH, consensus on factors that portend a worse outcome, and the best method or combination of methods of evaluation, remain lacking. In part this is due to the fact that IPAH is a rare and fatal disease. As a result the literature is dominated by small, often retrospective, studies with limited power to properly assess effects or compare multiple outcomes and draw meaningful conclusions. Thus conclusions from individual studies are difficult to draw and extrapolate to larger populations without a comprehensive view of the literature. Consensus statements have provided valuable guidance in the evaluation and management of IPAH patients but have not systematically reviewed the literature to provide a balanced overview of the evidence.[12,13] The purpose of this study is to systematically review the current medical literature to identify factors that prognosticate mortality in IPAH in an attempt to aid clinicians and health care professional in the appropriate evaluation and care of IPAH patients as well as identifying areas in need of further study. Furthermore, a comprehensive review of the literature will facilitate the development of clinically useful composite endpoints for clinical trials and therefore identification of these markers is important not only for patient care and epidemiologic research but also therapeutic clinical trials.