Prognostic value of multiple repeated biomarkers in pulmonary arterial hypertension associated with congenital heart disease

Pulmonary arterial hypertension (PAH) is a well-recognized complication of congenital heart disease (CHD), associated with alarmingly high morbidity and mortality. PAH-CHD is considered a complex syndrome involving many pathophysiological mechanisms, the components of which can be represented by various biomarkers.

There has been a growing interest in biomarkers as prognostic markers in chronic heart disease, given the wide availability and reproducibility, non-invasive nature and low costs. Although a wide variety of biomarkers have been explored in PAH-CHD, only natriuretic peptides have been incorporated by the European guidelines. The use of multiple biomarkers in combination (the so-called ‘multimarker’ approach) may however be of greater prognostic value than a single biomarker approach. Moreover, little is known about the prognostic value of repeatedly measured biomarkers. Ideally, changes in biomarker levels over time should reflect disease progression more accurately. We therefore evaluated the prognostic value of repeated measurements of several biomarkers in a prospective cohort of patients with PAH-CHD. Pathways and corresponding candidate biomarkers studied were (i) myocardial stress [N-terminal pro brain natriuretic peptide (NT-proBNP)], (ii) myocyte injury [high-sensitive troponin T (hs-TnT)], (iii) cardio-renal dysfunction (cystatin-C) and (iv) extracellular matrix remodelling (galectin-3).

This observational dual-centre study included consecutive PAH-CHD adults who were prospectively followed at our institutions with first clinical assessment between January 2004 and January 2016. According to local protocol, patients underwent routine evaluation every 6–12 months at outpatient clinics, including regular assessment of serum biomarkers using commercially available immunoassays. The endpoint was all-cause mortality. Patient deaths and causes of death were site determined and verified by medical records documentation. Biomarker levels were log-transformed and expressed as one standard deviation (SD) increase for hazard ratios (HRs) and 95% confidence intervals (CIs). The association with mortality was assessed using fitted mixed-effect, Cox regression and joint models, adjusted for age, gender and Eisenmenger syndrome (ES).

The study cohort consisted of 98 patients (43±16 years, 34% male, 37% Down syndrome), of whom 90% was treatment naive at baseline and started on advanced therapy within 1 month [interquartile range (IQR) 0.4–4.0]. The majority of patients had ES (69%), followed by closed defects (17%), systemic-to-pulmonary shunts (12%), and small defects (1%). Among ES patients, 47% had complex anatomy, 29% post-tricuspid shunts, and 24% post-tricuspid shunts. During a median follow-up of 6.9 (IQR 4.1–10.7) years, 41 patients (42%) died. Half of ES patients (47%) died at 50±12 years, whereas patients with systemic-to-pulmonary shunts (50%), closed defects (12%) or small defects (100%) died at older age (60±16, 66±16, and 77 years, respectively). Causes of death were validated in 38 (93%) cases, and primarily due to right heart failure (49%) and sudden cardiac death (12%). The average number of repeated measurements per patient during follow-up was nine for NT-proBNP, five for hs-TnT, and four for cystatin-C and galectin-3. Corresponding median levels of repeated measurements were: NT-proBNP 518 ng/L (IQR 223–1433), hs-TnT 11 ng/L (IQR 5–24), cystatin-C 0.97 mg/L (IQR 0.81–1.23), and galectin-3 15 μg/L (IQR 12–18). The correlations among the four biomarkers were weak to moderate (all r<0.4). All biomarker levels in patients who died progressively increased before time of death compared to those who remained alive during follow-up. Initiation of advanced therapy reduced biomarker levels in short-term, although levels deteriorated again after 1 year. After imputation and internal validation with 40 bootstrap samples, baseline levels were associated with an increased risk of death, HRs as follows: NT-proBNP 1.90 (95% CI 1.30–2.78); hs-TnT 1.54 (95% CI 1.14–2.08); cystatin-C 1.69 (95% CI 1.21–2.37); galectin-3 1.58 (95% CI 1.12–2.19). During follow-up, one SD increase in biomarker level represented 250% increase of NT-proBNP, 150% of hs-TnT, and 50% of cystatin-C and galectin-3. Each SD increase in biomarker level was associated with a doubled risk of death at any particular time (all P<0.001), adjusted HRs as follows: NT-proBNP 2.17 (95% CI 1.64–2.89); hs-TnT 2.34 (95% CI 1.61–3.41); cystatin-C 1.81 (95% CI 1.35–2.43); galectin-3 1.79 (95% CI 1.27–2.74). Risk prediction with repeated measurements was more accurate than with single measurements. Figure 1 illustrates the improved prognostic accuracy for an individual patient with NT-proBNP measurements; 95% CI is significantly broader using only the last single measurement compared with using repeated measurements. Of potential clinical value to physicians, we developed a free online risk stratification tool: https://biomarkers-pah-chd.shinyapps.io/PAH-CHDbiomarkers/.

We evaluated the prognostic value of a range of repeated biomarkers, individually and collectively, in patients with PAH-CHD. Our patient cohort had a high mortality rate, with 42% deceased by the end of follow-up. All repeated biomarkers individually were powerful predictors of mortality risk: patients with one SD increase had more than doubled the risk of death compared to those with no or less elevation. This is consistent with what has been found in previous studies in acquired heart failure that have shown that serial measures provide superior prognostic power over a single biomarker measurement. Previous studies have suggested using absolute cut-off values. From a clinical point of view, this approach may however neglect, at least to some extent, changes within a subject and not serve individual patients.
Contrary to studies in acquired heart failure, the most powerful prognostic biomarkers in time. Similar to data from acquired heart failure, repeated biomarker measurements were associated with an approximately two-fold higher mortality risk per SD increase and were more powerful predictors of mortality than single measurements. A multimarker approach provided no incremental prognostic value beyond the repeated measurements of individual biomarkers. Therefore, our findings support the concept of regular assessment of at least one biomarker, e.g. NT-proBNP, to help identify patients with PAH-CHD at greatest risk.

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**Conflict of interest**

None declared.

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