

### Prognostic value of serial measurements of NT-proBNP serum levels throughout the disease course in pediatric pulmonary arterial hypertension

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**Introduction:** N-terminal prohormone of brain natriuretic peptide (NT-proBNP), measured at time of diagnosis, has shown to be prognostic in children with pulmonary arterial hypertension (PAH) and treatment interventions are associated with changes in NT-proBNP levels. However, the prognostic value of serially measured NT-proBNP values has not been studied previously in PAH. We therefore aimed to determine whether serial measurements of NT-proBNP levels in children with PAH during the course of the disease have prognostic value for outcome and whether NT-proBNP levels throughout the disease course differ between survivors and non-survivors.

**Methods:** We included 82 pediatric PAH patients from the Dutch National Network for Pediatric Pulmonary Hypertension who had at least one follow-up measurement of NT-proBNP. The associations between serial measurements and concomitant variables known to represent disease severity were analyzed: World Health Organization-Functional Class (WHO-FC), 6-minute walking distance (6MWD), and tricuspid plane systolic excursion (TAPSE). Also, the courses of NT-proBNP levels were compared between survivors and non-survivors. Additionally, we determined optimal cut-off values of NT-proBNP to predict risk for adverse outcome during follow up. Outcome was defined as (heart-)lung transplantation-free survival.

**Results:** Higher NT-proBNP levels correlated with higher WHO-FC, lower 6MWD and lower TAPSE at any time during the disease course ( $p < 0.001$  for all analyses). Each unit increase in NT-proBNP ( $\log_{10}$  value) was associated with a 15.9 times higher risk for adverse outcome ( $p < 0.001$ ). A ten-fold increase in NT-proBNP level since baseline was associated with a 4.6 times increased risk of adverse outcome ( $p < 0.001$ ). Results remained significant after adjustment for age and sex. Non-survivors showed an exponential increase in NT-proBNP level over time in contrast to survivors who showed stable NT-pro-BNP levels ( $p = 0.005$ ) (see figure A and B). A cut-off value for NT-proBNP of 700 ng/l and 1400 ng/l showed best discrimination for risk for an event in the long-term and short-term respectively.

**Conclusions:** Higher serum NT-proBNP values throughout the disease course are associated with worse disease severity and adverse outcome in pediatric PAH. These results suggest that monitoring NT-proBNP levels supports decision making regarding treatment strategies in pediatric PAH.

