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A Serial NT-proBNP Model to Improve Prognostication in Patients with Pulmonary Arterial Hypertension

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Abstract

Background: Baseline elevation in N-terminal pro-brain natriuretic peptide (NT-proBNP) in pulmonary arterial hypertension (PAH) patients is associated with worse outcomes. Serial measurement of commonly available biomarkers could improve the precision of prognostic estimates and our understanding of PAH pathophysiology.

Methods: Included were 103 PAH patients with baseline elevated NT-proBNP prior to the initiation or escalation of therapy with at least two subsequent NT-proBNP measurements. Using patients' serial measurements, a linear mixed-effects model extrapolated a baseline NT-proBNP (intercept) and evolution (slope). These model-determined values were then used in Cox proportional hazards analysis to determine predictors of survival. Time-dependent area under the curve (AUC) analysis compared survival discrimination of serial versus single measurements of NT-proBNP.

Results: Subjects were 50 ± 14 years; most had idiopathic PAH, congenital heart disease, or connective tissue disease. Survivors were younger than non-survivors 47 ± 14 versus 55 ± 12 years (p=0.002). A multivariable survival model using invasive and non-invasive covariates found NT-proBNP significantly predicted mortality. Time-dependent AUC was significantly greater for modeled (intercept) versus measured NT-proBNP.

Conclusions: Prognostic modeling utilizing serial NT-proBNP measurements better predict survival than a single baseline value. This evidence supports the conduct of future studies of serial measurement of NT-proBNP to further clarify its role in the clinical care of PAH patients.

Keywords: Biomarker; Pulmonary arterial hypertension; Right heart failure; NT-proBNP; Survival

Abbreviations: AA: Anorexigen Associated; AUC: Area Under the Curve; CCB: Calcium Channel Blocker; CI: Cardiac Index; CO: Cardiac Output; CHD: Congenital Heart Disease; CTD: Connective Tissue Disease; ERA: Endothelin Receptor Antagonist; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; IPAH: Idiopathic Pulmonary Arterial Hypertension; IQR: Interquartile Range; IV: Intravenous; L: Liters; m: meters; mPAP: mean Pulmonary Artery Pressure; mRAP: mean Right Atrial Pressure; METs: Metabolic Equivalents; min: minute; mmHg: millimeters of mercury; mo: months; NT-proBNP: N Terminal pro Brain Natriuretic Peptide; PAH: Pulmonary Arterial Hypertension; PDE5-I: Phosphodiesterase type-5 inhibitor; pg/ml: picograms/milliliter; PA sat: Pulmonary Arterial saturation; PCWP: Pulmonary Capillary Wedge Pressure; PG: Prostaglandin; PHC: Pulmonary Hypertension Connection; PVOD: Pulmonary Veno-Occlusive Disease; PVR: Pulmonary Vascular Resistance; RV: Right Ventricle; sat: saturation; SQ: Subcutaneous; WHO FC: World Health Organization Functional Class

Introduction

Pulmonary arterial hypertension (PAH) is a rare disease characterized by a progressive increase in pulmonary vascular resistance with resultant right ventricular (RV) maladaptation, failure, and death [1]. The indirect and direct measurement of RV function at the time of diagnosis with invasive and non-invasive methods has proved useful for predicting survival in PAH patients [2-4]. Specifically, baseline elevations in N-terminal pro-brain naturetic peptide (NT-proBNP), a peptide released by ventricular myocytes under stretch and a marker of underlying hemodynamic stress [5,6], predicts worse functional status, invasive pulmonary hemodynamics, and overall survival [3,4,7-9]. Most of these studies focus exclusively on baseline parameters, with the utility of serial quantitative measurements to predict survival remaining uncharacterized [9].

Recent studies suggest potential advantages for serial measurement in clinical care of PAH patients. Among clinically stable idiopathic PAH (IPAH) patients over a five-year period, serial increase in RV volume preceded eventual clinical worsening [10]. Mauritz et al. incorporated serial NT-proBNP measurements into survival prediction and found that temporal changes in this biomarker added information beyond that of a single baseline value [7]. Given the paucity of studies

on serial trends with easily obtainable measurements, the aim of the current study was:

1. To evaluate the prognostic utility of incorporating serial measurements of NT-proBNP into survival prediction in patients with PAH and
2. To identify patient-specific factors that modify the odds of survival. We hypothesized that serial measurements of NT-proBNP would provide better survival prediction than a single baseline measurement.

Methods

Study population

From a total of 576 patients in the Pulmonary Hypertension Connection (PHC) database we retrospectively identified a cohort of 103 WHO Group I PAH patients with elevated baseline NT-proBNP. The inclusion criteria were: a baseline NT-proBNP (>125 pg/mL for age <75, >450 pg/mL for age >75) prior to either

1. The initiation or
2. The escalation of therapy and at least 2 serial measurements of the biomarker.

All patients required a baseline cardiac catheterization up to 12 weeks after their initial NT-proBNP measurement. Patients were not enrolled if there was a change in clinical status in this time period. Those with baseline normal NT-proBNP or those not meeting the time interval for catheterization were excluded. See Figure 1 for a graphical depiction of patient selection.

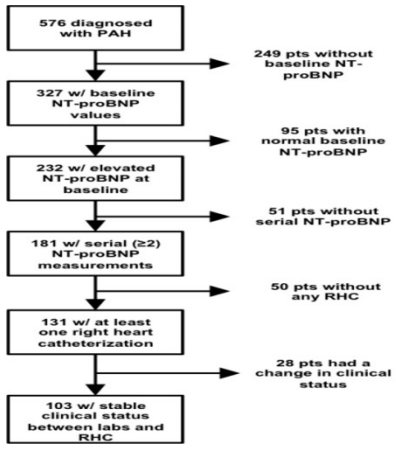

Figure 1: Patient selection flowchart.

The database was initiated in March 2004 with patients retrospectively enrolled before this date from 1982, and prospectively enrolled thereafter [10]. The patient with the earliest date of enrollment in this study was October 6, 2003– the date of the first available serial NT-proBNP measurement. The PHC registry was and continues to be approved by the University of Chicago Institutional Review Board (Approval Number: IRB13-1368) with all patients providing written informed consent.

Objective measures collected

The treating physician assigned the baseline World Health Organization functional class (FC). A Naughton-Balke protocol treadmill test measured baseline exercise capacity and was reported as metabolic equivalents (METs) [11]. Either one of the PH staff or the outpatient phlebotomy team collected serum for NT-proBNP at the time of the clinic visit.

Statistical analysis

Statistical analysis was performed in the R software environment (R Core Team 2013, http://www.r-project.org, library survival, time ROC, nlme). All variables were confirmed to have a normal distribution graphically and using the Shapiro-Wilkes test; NT-proBNP values were not normally distributed and therefore logarithmically transformed prior to statistical analysis.

To determine the potential utility of serial NT-proBNP measurements, we utilized a two-step modeling process similar to that previously implemented by Mauritz et al. [7]. Briefly, this methodology utilized a linear mixed-effects model using all serial NT-proBNP measurements to calculate (1) an intercept (extrapolated "baseline" NT-proBNP value) and (2) slope (rate of change of NT-proBNP) for each patient. The biological motivation of this modeling technique is discussed in more detail by Mauritz et al. [7]. Baseline NT-proBNP and model-derived intercepts and slopes were then used as covariates in multivariable Cox proportional hazards analyses while adjusting for non-invasive baseline variables only (age, gender, WHO FC, and estimated glomerular filtration rate (eGFR) or both non-invasive and invasive (mPAP, mRAP, and CI) baseline variables together. The proportional hazards assumption was confirmed in 'R' graphically and numerically. Discrimination performance of the multivariable models is reported as concordance or Harrell's C statistic [12,13].

Time-dependent area under the curve (AUC) analysis was performed using the two model-derived covariates (intercept, slope) and the measured baseline NT-proBNP to compare survival discrimination annually from years one through five following the baseline NT-proBNP measurement. Sub-group time-dependent AUC analyses were then performed after separating patients into four groups based on a patient's slope (positive/worsening or negative/improving) and if their intercept was above or below the actual measured baseline NT-proBNP. Only patients with a negative slope were included in our sub-group analysis; eight patients had positive slopes. This sub-group analysis was performed for exploratory purposes to determine if survival discrimination was better in a sub-group with a specific slope and intercept combination and if so, what their contribution was to the overall analysis. Kaplan-Meier survival was based on data collected through February 22nd, 2014.

Results

Baseline characteristics

Table 1 summarizes the baseline demographic, functional class, hemodynamics, and blood studies for the entire cohort and the sub-categories of patients surviving through the enrollment period. Women made up 78% of the cohort with an average age of 50 ± 14 years. Survivors were significantly younger than non-survivors 47 ± 14 versus 55 ± 12 years (p=0.002) at the time of their baseline NT-proBNP measurements. Patients predominantly carried the diagnosis of

connective tissue disease, idiopathic PAH, or congenital heart disease. There was no significant difference in baseline hemodynamics, functional class, or blood gas values. Baseline NT-proBNP was significantly lower in the survivor group (median+interquartile range (IQR)) 1448 µg/ml (552-3171) versus 2500 µg/ml (1323-4131), p=0.01. Median time of follow-up for all patients was 28.8 months (12.6-51.2), among survivors was 38.0 months (14.2-60.7), and for non-survivors was 15.6 months (7.62-28.9); (median+IQR).

Variable	Total (N=103)	Survivors (N=71)	Non-survivors (N=32)
Age	50 ± 14	47 ± 14	56 ± 12
Female	80	57	23
Etiology:			
CHD	15	13	2
CTD	35	17	18
AA	4	3	1
HIV	2	2	0
PP	8	2	6
Idiopathic	31	27	4
Familial	6	5	1
PVOD	2	2	0
WHO FC, N=93		N=61	N=32
II	9 (10%)	6 (9%)	3 (9%)
III	73 (78%)	48 (79%)	25 (78%)
IV	11 (12%)	7 (12%)	4 (13%)
Mean ± SD	3.02 ± 0.47	3.02 ± 0.47	3.03 ± 0.47
METs, N=52	4.65 ± 2.05	5.13 ± 2.05, N=40	3.08 ± 1.00, N=12
Hemodynamics			
Heart rate	80 ± 13, N=83	78 ± 12, N=57	82 ± 15, N=26
mRAP (mmHg)	9.3 ± 5.6, N=90	9.1 ± 5.6, N=61	9.8 ± 5.7, N=29
mPAP (mmHg)	51 ± 10, N=91	50 ± 10, N=62	52 ± 10, N=29
PCWP (mmHg)	10 ± 3.9, N=87	10 ± 3.8, N=59	10 ± 4.4, N=28
CO (L/min)	4.1 ± 1.5, N=88	4.2 ± 1.6, N=60	3.8 ± 1.3, N=28
CI (L/min/m^2)	2.1 ± 0.7, N=87	2.2 ± 0.7, N=59	2.1 ± 0.6, N=28
PVR (Woods Units)	11 ± 5, N=89	11 ± 4.9, N=60	12 ± 4.8, N=29
Blood gases			
Arterial sat (%)	92 ± 4.5, N=69	92 ± 4.1, N=48	93 ± 5.4, N=21
PA sat (%)	60 ± 12, N=90	60.5 ± 12, N=61	59 ± 10, N=29
NT-proBNP (log_{10}, pg/mL)	3.2 ± 0.48	3.1 ± 0.47	3.4 ± 0.45
NT-proBNP (pg/mL)*	1778 (628-3407)	1448 (552-3171)	2500 (1323-4131)
Therapies at baseline	N (%)	N (%)	N (%)
None	48 (46.6%)	33 (47%)	15 (47%)
One	44 (42.7%)	28 (39%)	16 (50%)
Two	11 (10.7%)	10 (14%)	1 (3%)
Therapy breakdown			
CCB	2 (2%)	2 (3%)	0 (0%)
PDE5-I	87 (84%)	60 (85%)	27 (84%)
PG (IV/SQ)	45 (44%)	27 (38%)	18 (56%)
PG (inhaled)	11 (11%)	6 (9%)	5 (15%)
ERA	29 (28%)	22 (31%)	7 (21%)
Follow-up (mo)*	28.8 (12.6-51.2)	38.0 (14.2-60.7)	15.6 (7.62-28.9)

Table 1: Baseline patient characteristics with variables presented as mean ± standard deviation or *Presented as median (inter-quartile range); CHD: Congenital Heart Disease; CTD: Connective Tissue Disease; AA: Anorexigen Associated; HIV: Human Immunodeficiency Virus; PVOD: Pulmonary Veno-Occlusive Disease; WHO FC: World Health Organization Functional Class; METs: Metabolic Equivalents, mRAP: mean Right Atrial Pressure; mPAP: mean Pulmonary Artery Pressure; PCWP: Pulmonary Capillary Wedge Pressure; CO: Cardiac Output; CI: Cardiac Index; PVR: Pulmonary Vascular Resistance; sat: saturation; PA sat: Pulmonary Arterial saturation; mmHg: millimeters of mercury; L: Liters, m: meters; CCB: Calcium Channel Blocker; PDE5-I: Phosphodiesterase type-5 inhibitor; PG: Prostaglandin; IV: Intravenous; SQ: Subcutaneous; ERA: Endothelin Receptor Antagonist; mo: months.

NT-proBNP measurements

Patients had between 2 and 18 serial NT-proBNP values measured at irregular time intervals in both the chronic and acute phases of his/her PAH treatment. The minimum time-interval between two samples was 1-day. See Figure 2 for a histogram of the number of NT-proBNP samples per patient.

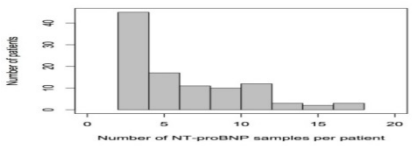

Figure 2: Histogram of NT-proBNP sample number and frequency.

Cox proportional hazards analysis

Table 2A depicts the results of adjusted multivariable Cox proportional hazards (adjustment for non-invasive clinical variables).

After adjusting for age, gender, WHO FC, and eGFR, NT-proBNP remained a significant independent predictor of mortality with HR: 3.02 (1.25-7.31), p=0.014. Adjusting for the same variables and using model intercepts and slopes, in place of NT-proBNP, the intercept, or variation free baseline, was found to be a significant independent predictor of mortality with HR: 4.07 (1.17-14.2), p=0.027; slope was not significant with HR: 1.07 (0.97-1.17), p=0.18. While the slope was not a predictor of survival, the intercept was, consistent with the idea incorporation of serial NT-proBNP values into models of prognostication provided meaningful clinical discrimination.

Variable	HR (95% CI)	p-value	Concordance (SE)	Model #
NT-proBNP	3.02 (1.25-7.31)	0.014	0.762 (0.055)	1
Slope	1.07 (0.97-1.17)	0.175	0.821 (0.055)	2
Intercept	4.07 (1.17-14.2)	0.027		

Table 2A: Multivariable cox proportional hazards analysis (non-invasive variables only) with hazard ratios, 95% confidence interval, and p-values. (A) measured NT-proBNP (B) intercept and slope.

Repeating our Cox multivariable analyses (Table 2B) adjusting for both non-invasive and invasive (mPAP, mRAP, CI) we again found that intercept remained a significant, independent predictor of mortality with HR: 4.14 (1.04-16.8), p=0.0445. Neither slope nor baseline NT-proBNP were significant in the multivariable Cox model utilizing both non-invasive and invasive baseline variables.

Variable	HR (95% CI)	p-value	Concordance (SE)	Model #
NT-proBNP	2.32 (0.85-6.36)	0.102	0.795 (0.06)	1
Slope	1.04 (0.94-1.16)	0.41	0.837 (0.06)	2
Intercept	4.14 (1.04-16.8)	0.0445		

Table 2B: Multivariable cox proportional hazards analysis (non-invasive and invasive variables) with hazard ratios, 95% confidence interval, and p-values. (A) measured NT-proBNP (B) intercept and slope.

Time dependent AUC analysis

Time-dependent AUC is plotted in Figure 3A for measured NT-proBNP, intercept, and slope. The AUC was significantly greater for intercept versus measured NT-proBNP at year 1 (0.73 *vs.* 0.62, p=0.045), year 3 (0.84 *vs.* 0.75, p=0.015), and year 4 (0.78 *vs.* 0.68, p=0.01).

Time-dependent AUC analysis is displayed in Figure 3B for the sub-group of patients with a negative slope and an intercept less than (below) their measured baseline NT-proBNP (66 patients). At year 1, the AUC was significantly greater using intercept versus baseline NT-proBNP (0.85 *vs.* 0.73, p=0.009) (Figure 4).

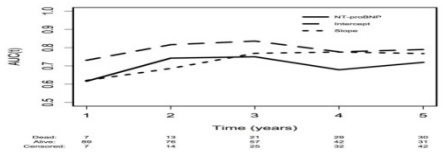

Figure 3A: Time-dependent AUC for NT-proBNP, intercept, and slope in the figure with number of patients dead, alive, and censored at each time point at the bottom of the figure.

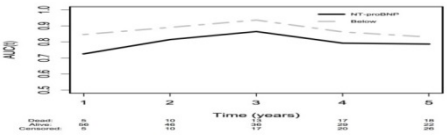

Figure 3B: Time-dependent AUC analysis comparing the sub-group of patients with a negative slope and an intercept less than (below) their measured baseline NT-proBNP value (66 patients); likewise, the number of patients dead, alive, and censored at each time point is shown at the bottom of the figure.

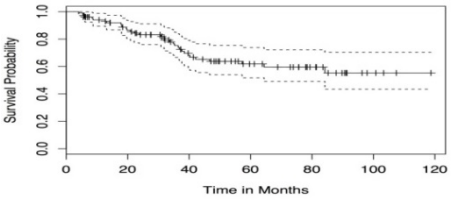

Figure 4: Kaplan-Meier survival estimate with 95% confidence intervals (dashed lines) of survival, from the time of baseline serum NT-proBNP measurement for all patients.

Discussion

In this cohort of PAH patients with baseline elevated NT-proBNP, we found that a model-based assessment of a patient's serial NT-proBNP measurements improved survival discrimination compared to using a single NT-proBNP value. These findings provide evidence to support further evaluation of the role of serial NT-proBNP measurements in the long-term care of PAH patients.

Our findings are consistent with those of Mauritz et al. that incorporating serial NT-proBNP measurements into prognostication provide additional information over that of a single baseline measurement [7]. Additionally, with this linear mixed-effects modeling strategy we demonstrated in our time-dependent AUC analysis that improvements in survival discrimination persist over time, again providing support for a more detailed evaluation of the role for serially measuring NT-proBNP in PAH patients. As such, serial changes in NT-proBNP may be an important clinical variable to follow in addition

to being a predictor of survival at baseline. We believe that NT-proBNP measurement should not be used in isolation. With further validation, these results suggest that in the absence of any overt change in a patient's self-reported health, a serial increase in a patient's NT-proBNP might lead the treating physician to consider more intensive clinical evaluation, therapy modification, and/or therapy intensification.

These observations on serial assessment of NT-proBNP are consistent with the concept of RV "health" described by Van de Veerdonk et al. where the investigators found that a serial increase in RV volume on cardiac magnetic resonance imaging preceded ultimate clinical deterioration [15]. NT-proBNP is a more practical and cost effective measure to follow in clinical practice and in some cases may provide similar information in the management of PAH patients.

Limitations

Given the limited availability of METS data for our cohort (only 52/103 patients had baseline METS data available), we could not assess the relevance of baseline exercise capacity in our multivariable analysis. Additionally, not all serum studies were drawn on the same day as the patient's baseline invasive hemodynamic measurements. Our analysis does not address the question of how frequently a patient should have their NT-proBNP checked. This study also did not evaluate the relationship of NT-proBNP to other objective outcomes such as time to clinical worsening or benefit. Based on our findings these will need to be addressed more fully in future investigations.

Conclusion

Serial NT-proBNP measurement provides additional survival information beyond that of a single measurement. Our findings provide evidence to support continued evaluation, both retrospective and prospective, of the role of serial NT-proBNP measurements in the long-term clinical care of PAH patients. We recommend that these studies focus specifically on sampling frequency and potential treatment goals for reductions in NT-proBNP.

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Author contributions: AMW had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. AMW, MLM, and MGM contributed to the data analysis and interpretation, drafting and critical review of the manuscript, and approval of the final version. VT and CG contributed to the acquisition and organization of the raw data.

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