Prognostic Value of the Baseline Serum Sodium Level in 2 Independent Cohorts of Pulmonary Arterial Hypertension

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Introduction:

Hyponatremia has prognostic value in heart failure and liver disease, so we studied the potential prognostic value of hyponatremia in pulmonary arterial hypertension (PAH).

Methods:

We performed secondary analyses of 2 PAH cohorts: 1) United Therapeutics' randomized clinical trials (including P0:03, P0:04, P0:05, & P0:06), and 2) A long-term PAH registry at the Cleveland Clinic. We included adult WHO group 1 PH patients. Our hypothesis was that baseline hyponatremia is associated with worse 1-year survival.

Results:

Baseline Na level is negatively correlated with baseline mean right atrial pressure (r= -0.09; p=0.018; r=-0.089 p=0.015 in cohorts #1 and 2 respectively). In unadjusted analyses of cohort #1, sodium level (as a continuous variable) is associated with 1-year mortality (Hazard ratio=0.94; p=0.035). Hyponatremia (Na $\leq$137) status loses its significance (p=0.12) in the multivariable regression Cox model when adjusted for functional class (after applying a stepwise model selection procedure to identify the confounding variable whose presence turns the effect of baseline sodium level into insignificant). Secondary analyses using a cut-off value of $\leq$ 135 mmol/liter to define hyponatremia and looking at 2-, 3-, and 4-year mortality showed overall similar results.

These results were validated in cohort #2, which suggested the association between hyponatremia and survival is driven by poor outcomes among patients below a very low sodium cutoff of $\leq$130. Although the sample size for patients with severe hyponatremia (Na $\leq$130) was small (31 patients), severe hyponatremia in the validation cohort was associated with poorer overall survival (53% versus 77%; p=0.01), and that the statistical significance of the association at this cutoff holds up under covariate adjustment for age, functional class, and baseline 6-minute walk distance (p<0.001).

Conclusion:

Although baseline hyponatremia is associated with 1-year mortality, it loses its significance when adjusted for functional class in the multivariable regression Cox model.

	Cohort #1			Cohort #2		
	Na ≥ 138	Na ≤ 137	p-value	Na ≥ 138	Na ≤ 137	p-value
Total # of patients	636	184	N/A	543	248	N/A
Sodium level	141	135	<0.001	141	134	<0.001
Age (years)	46 ± 14	49 ± 13	0.020	57 ± 15	53 ± 14	<0.001
Female gender (%)	79%	75%	0.321	74%	65%	0.009
Caucasian Race (%)	84%	79%	0.041	84%	79%	0.14
PAH etiology: Idiopathic CTD	 53% 21%	 55% 21%	0.556	 41% 29%	 29% 29%	0.008
Mean 6MWD (meters) at baseline	331 ± 86	322 ± 89	0.282	313 ± 117	298 ± 105	0.11
Baseline NYHA/WHO functional class IV	7%	17%	<0.001	17%	22%	0.26

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