Research Article

Is hyponatremia associated with mortality in pulmonary arterial hypertension?

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Abstract

Hyponatremia is associated with poor prognosis in left heart failure and liver disease. Its prognostic role in pulmonary arterial hypertension (PAH) is not well defined. We investigated the association between hyponatremia and one-year mortality in two large cohorts of PAH. This study is a secondary analysis evaluating the association between hyponatremia and one-year mortality in patients treated with subcutaneous treprostinil (cohort 1). The results are validated using a PAH registry at a tertiary referral center (cohort 2). Eight-hundred and twenty patients were enrolled in cohort 1 (mean age $= 47 \pm 14$ years) and 791 in cohort 2 (mean age $= 55 \pm 15$ years). Sodium level is negatively correlated with 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, the sodium level (as a continuous variable) is associated with one-year mortality (hazard ratio $= 0.94$; $P = 0.035$). Hyponatremia loses its significance (as a continuous variable and when dichotomized at ≤ 137 mmol/L; $P = 0.12$) when adjusted for functional class (FC), which is identified as the variable whose presence turns the effect of sodium level into non-significant. Secondary analyses using a cut-off value of < 135 mmol/L showed similar results. These results are validated in cohort 2. Although the sample size for patients with sodium < 130 mmol/L is small ($n = 31$), severe hyponatremia is associated with higher overall mortality (47% versus 23%; $P = 0.01$), even when adjusting for age, FC, and baseline 6-min walk distance ($P < 0.001$). Although baseline hyponatremia is associated with one-year mortality, it loses its significance when adjusted for FC.

Keywords

pulmonary hypertension, pulmonary arterial hypertension, hyponatremia, prognosis, mortality

Introduction

Pulmonary arterial hypertension (PAH) is a diffuse pulmonary vasculopathy involving all three layers of the arteriolar wall, leading to progressive narrowing of the vessels lumen, which results in elevated pulmonary arterial resistance.[1,2] PAH belongs to World Health Organization (WHO) group 1 pulmonary hypertension (PH), which includes idiopathic PAH, heritable PAH, connective tissue disease- associated PAH (CTD-PAH), congenial heart disease-associated PAH (CHD-PAH), portopulmonary hypertension (PoPH), and PH associated with HIV, schistosomiasis, anorexic drugs, and toxins.[3] Per the

REVEAL registry (Registry to Evaluate Early and Long-Term PAH Disease Management), the one-year survival rate of PAH patients after diagnosis is 85%, while three-, five-, and seven-year survival rates are only 68%, 57%, and 49%, respectively.[4] Prognostication is important in these patients to guide aggressiveness of treatment and discussions on goals of care. Prognosis of PAH patients depends on

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several clinical and laboratory characteristics, including co-morbidities and functional status.[5]

Hyponatremia is typically caused by excess of water relative to sodium. Hyponatremia is an established biomarker of poor prognosis in left-sided heart failure[6–9] and liver cirrhosis.[10–13] In both conditions, hyponatremia is triggered by a decrease in effective arterial volume leading to activation of the renin-angiotensin-aldosterone system (RAAS), resulting in increase in aldosterone and anti-diuretic hormone. There are several small studies that reported a worse prognosis of hyponatremia in PAH.[14–18] All these studies had significant limitations, such as limited sample sizes and lack of adjustment for relevant co-variables, thus requiring further validation in larger cohorts. The objective of this study is to further evaluate the association between hyponatremia and one-year mortality in two independent, different, and large PAH cohorts.

Methods

The characteristics of the two PAH cohorts included in this study have been described elsewhere.[19] In summary, cohort 1 included adult PAH patients enrolled in prospective placebo-controlled clinical trials of subcutaneous treprostinil infusion. Patients were eligible de novo or rolled over from either a placebo-controlled pilot study or a large placebo-controlled randomized study. These patients were then followed long-term, and long-term outcomes including vital status were reported. Cohort 2 patients were patients enrolled into a PAH registry at a tertiary referral PH center, at the Cleveland Clinic in Ohio.

Only adult patients with PAH (WHO group 1 PH) with available baseline sodium levels were included in this analysis. All patients underwent right heart catheterization (RHC) and had evidence of PAH characterized by a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units (WU) in cohort 1; some patients in cohort 2 had PAWP > 15 mmHg but were deemed to be WHO group 1 PH per the treating PH expert. Two PH experts reviewed the information available and agreed on the PAH etiology based on current guidelines.

The advantages and disadvantages of these cohorts are self-evident, the first cohort being a select group of PAH patients who had to satisfy strict inclusion and exclusion criteria to be enrolled in a clinical trial, and the second one representing typical PAH patients seen in everyday practice, albeit in an experienced tertiary referral center. More specifically, patients enrolled in a clinical trial tend, generally speaking, to be more "homogeneous" and with fewer co-morbidities and are not at either extreme regarding the severity of their disease or overall survival expectation (when compared to a registry population such as cohort 2, or when compared to a "real-life" patient population whether at an academic teaching center or community-based practice,

where many of these patients will not satisfy the inclusion/exclusion criteria of the trials and/or would not consent to be enrolled in a research study [trial or registry]).

For the purposes of this study, hyponatremia, or low sodium level, was defined as sodium concentration at ≤ 137 mmol/L (see the "Discussion" section below). Severe hyponatremia was defined as sodium concentration at ≤ 130 mmol/L. All sodium levels included in these analyses are the baseline measured values at the time of entry into the clinical trials for cohort 1 and at first evaluation for PH for cohort 2.

Statistical analysis

Sample descriptive data were expressed as mean ± standard deviation and categorical data were expressed as counts (percentages). Two-sample Student's t-test was used to compare means of continuous variables for normally distributed data between two groups, while Wilcoxon's rank-sum test was used to compare non-normally distributed data between two groups. Spearman correlation coefficient (r) was used to assess association between continuous (or categorical) variables. Linear regression and proportional hazard, both simple and multiple models were used to evaluate the association between different variables and mortality endpoint. Our multiple regression model included the following co-variables: PAH-specific treatment, sodium level, gender, PAH etiology, age, baseline 6-min walk distance (6MWD), BORG index, and functional class (FC).

We applied a step-wise model selection procedure to identify a reduced model adjusting for age, 6MWD, and FC. We then compared a simple model (including sodium level only) and multiple models (including both sodium level and one of the confounding variables, specifically age, 6MWD, or FC) to find out if the presence of any of the variables makes the effect of the sodium level non-significant.

The primary outcome was one-year mortality and the primary parameter of interest was sodium level as a continuous variable. Secondary analyses were done including two-, three-, and four-year mortality, as well as using a dichotomized sodium level using different thresholds to define hyponatremia, as done in previous reports.[6–8,10–12] We hypothesized that baseline sodium level (as a continuous variable or dichotomized at 137 mmol/L [as shown in the liver failure and left heart failure literature])[6–8,10–12] is associated with one-year mortality.

The institutional review board at Yale University (IRB Protocol No. 1312013166) approved these de-identified analyses.

Results

Patient characteristics

The 820 and 791 adult PAH patients who comprise cohort 1 (mean age = 47 ± 14 years) and cohort 2

(mean age $= 55 \pm 15$ years), respectively, are mostly Caucasian women (Table 1). The largest proportion of patients in both cohorts had idiopathic PAH. The mean 6MWD was 329 ± 87 in cohort 1 and 309 ± 114 in cohort 2, respectively, suggesting moderate functional impairment.

In cohort 1, the mPAP is 59 ± 15 mmHg with an elevated PVR at 13.5 ± 7 WU. In cohort 2, the mPAP is 49 ± 15 mmHg with PVR at 9.3 ± 5.9 WU. Although there are no differences in cardiac index (CI), PAWP, or PVR between groups with normal and low sodium levels in the two cohorts, mean right atrial pressure (mRAP) is significantly lower (9.9 versus 11.5 mmHg in cohort 1; and 10.1 versus 11.7 mmHg in cohort 2) in the group with sodium > 137 mmol/L in both cohorts 1 ($P = 0.04$) and 2 ($P = 0.004$). In addition, the pulmonary artery pulsatility index (PAPi) is significantly lower in the low sodium group in both cohort 1 ($P = 0.04$) and cohort 2 ($P = 0.005$).

In cohort 1, 184 patients (22.4%) have hyponatremia (Fig. 1). The patients with hyponatremia are older ($P = 0.02$), have a higher proportion of New York Heart Association (NYHA) or WHO FC IV ($P < 0.001$), have higher mRAP ($P = 0.036$) and higher RAP/PAWP ratio ($P = 0.038$), and lower baseline right ventricular stroke work index (RVSWI) ($P = 0.017$) (Table 1). There is a weak association between hyponatremia and NYHA FC ($r = -0.15$; $P < 0.0001$).

In cohort 2, patients with hyponatremia are younger ($P < 0.001$), 35% of them are men (versus 26% in the normo-natremia group; $P = 0.009$), and they have a lower baseline PAPi ($P = 0.005$) (Table 1). There is also a weak association between hyponatremia and NYHA FC ($r = -0.14$; $P < 0.0001$).

The baseline sodium level is negatively associated with baseline mRAP ($r = -0.09$, $P = 0.018$; $r = -0.089$, $P = 0.015$ in cohorts 1 and 2, respectively). There is no significant difference in sodium level among the different PAH subgroups (139, 139, 140, and 139 mmol/L for idiopathic PAH, CTD-PAH, CHD-PAH, and PoPH, respectively).

Table 1. Patients' demographics and characteristics.

	Cohort 1 (n = 820 patients)			Cohort 2 (n = 791 patients)		
	Na ≥ 138 mmol/L	Na ≤ 137 mmol/L	P value	Na ≥ 138 mmol/L	Na ≤ 137 mmol/L	P value
Total patients (n)	636	184	N/A	543	248	N/A
Age (years)	46 ± 14	49 ± 13	0.02	57 ± 15	53 ± 14	<0.001
Female gender (%)	79	75	0.32	74	65	0.009
Caucasian race (%)	84	79	0.04	84	79	0.14
PAH etiology			0.56			0.008
Idiopathic (%)	53	55		41	29	
CTD (%)	21	21		29	29	
CHD (%)	22	16		15	15	
PoPH (%)	4.4	7.6		8	19	
Mean 6MWD (m)	331 ± 86	322 ± 89	0.28	313 ± 117	298 ± 105	0.11
BORG dyspnea index	4.3 ± 2.4	4.5 ± 2.3	0.41	Not collected	Not collected	Not applicable
FC III (%)	77	72	<0.001	49	52	0.26
FC IV (%)	7	17		17	22	
Cardiac index	2.3 ± 0.8	2.3 ± 0.7	0.60	2.6 ± 0.9	2.6 ± 1.0	0.34
RAP (mmHg)	9.9 ± 5.5	11.5 ± 6.9	0.04	10.1 ± 6.1	11.7 ± 6.8	0.004
mPAP (mmHg)	59 ± 16	56 ± 14	0.025	50 ± 15	49 ± 14	0.31
PAWP (mmHg)	9.4 ± 3.5	9.6 ± 3.8	0.65	12.7 ± 7.1	13.3 ± 7.4	0.28
PVR (WU)	13.7 ± 6.7	12.8 ± 6.3	0.26	9.5 ± 6.0	8.7 ± 5.8	0.06
RAP/PAWP ratio	1.2 ± 0.8	1.3 ± 0.8	0.04	0.9 ± 0.7	1.0 ± 0.9	0.14
RVSWI	1.4 ± 0.8	1.2 ± 0.5	0.02	16.6 ± 8.2	17.3 ± 7.6	0.26
Pulmonary artery compliance	1.1 ± 0.6	1.1 ± 0.6	0.66	1.5 ± 1.1	1.7 ± 1.3	0.14
PAPi	7.9 ± 7.2	6.9 ± 6.3	0.04	6.8 ± 6.4	5.7 ± 5.2	0.005
Sodium level	141	135	<0.001	141 ± 2	135 ± 3	<0.001

All reported measurements are at baseline.
CTD, connective tissue disease; CHD, congenital heart disease with systemic-to-pulmonary shunts; PoPh, portopulmonary hypertension; 6MWD, 6-min walk distance; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; PAPi, pulmonary artery pulsatility index; FC, functional class.
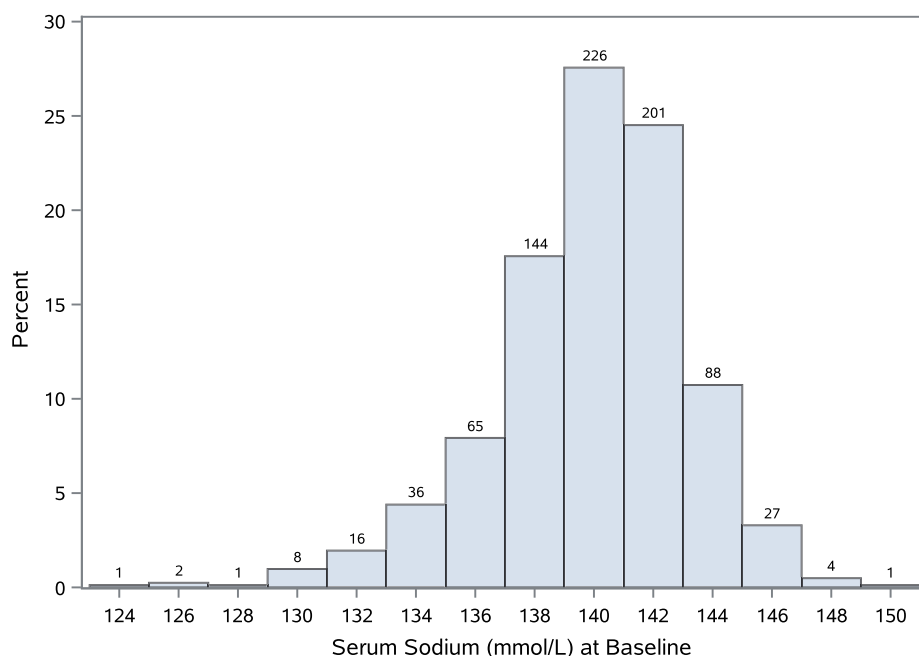
Fig. 1. Histogram showing the frequency of patients with different sodium levels in cohort 1.

Mortality analyses

In unadjusted analyses of cohort 1, sodium level (as a continuous variable) is associated with one-year mortality (hazard ratio [HR] = 0.94; $P = 0.035$). Hyponatremia (sodium ≤ 137 mmol/L) status loses its significance ($P = 0.12$) in the multivariable regression Cox model when adjusted for FC. Secondary analyses (identified a prioi; results not shown) using a cut-off value of ≤ 135 mmol/L to define hyponatremia and looking at two-, three-, and four-year mortality show overall similar results. Post-hoc secondary analyses excluding PoPH patients did not change the results of these analyses either.

Although baseline hyponatremia is associated with one-year mortality, it loses its significance after adjustment for 6MWD ($P = 0.06$) or FC ($P = 0.18$). FC is the predominant variable that neglected the association with one-year mortality.

Subgroup analyses of PAH patients with CTD in cohort 1 show no difference in the association between hyponatremia and mortality in the CTD versus the non-CTD PAH patients (interaction item P value = 0.84), or the scleroderma-PAH versus non-scleroderma-PAH patients (interaction item P value = 0.98). Similarly, there was no difference in the association between hyponatremia and mortality in the subgroup of patients originally randomized to treprostinil versus those randomized to placebo during the short-period period of the original trial (interaction item P value = 0.42), before all being placed on treprostinil long-term (it should be noted that there was no statistically significant difference in the achieved treprostinil dose between these two subgroups by the end of the open label study).
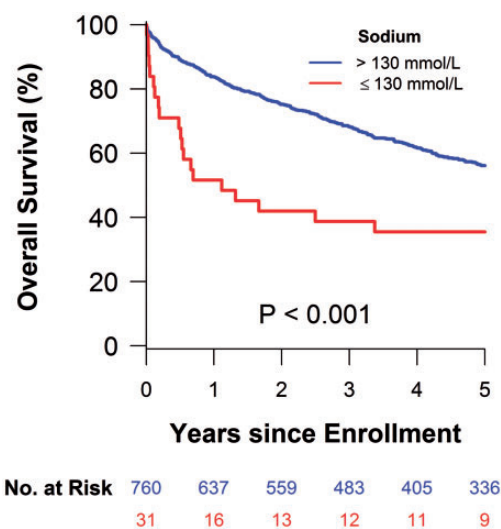

Fig. 2. Kaplan–Meier survival curve showing a statistically significant difference in survival between the group of PAH patients in cohort 2 with sodium < 130 versus > 130 mmol/L.

These results were validated in cohort 2. The unadjusted HR for hyponatremia (sodium ≤ 137 mmol/L) is 0.80 (95% confidence interval = 0.63–1.00). There is no association between hyponatremia and one-year mortality in cohort 2 in the multivariable regression model ($P > 0.05$). Although the sample size for patients with severe hyponatremia (sodium ≤ 130 mmol/L) is small (31 patients), severe hyponatremia in the validation cohort is associated with

higher mortality (47% versus 23%; $P = 0.01$), and the statistical significance holds up when adjusted for age, NYHA FC, and baseline 6MWD ($P < 0.001$) (Fig. 2). As a post-hoc secondary analysis, there is no difference in the above cohort 2 results when only patients with a PAWP ≤ 15 mmHg are included in the analysis. There are only 12 patients in cohort 1 with sodium of ≤ 130 mmol/L, so an adjusted analysis of this group is not feasible.

Discussion

This study shows an association between hyponatremia and mortality in two large PAH cohorts; however, this association loses its statistical significance when adjusted for relevant variables, especially the FC. In cohort 2, we show that severe hyponatremia (sodium ≤ 130 mmol/L) remains a strong predictor of one-year mortality even when adjusted for relevant co-variables. This included the largest PAH cohorts reported in the literature evaluating this association.

Correlation between hyponatremia (sodium ≤ 137 mmol/L) and one-year mortality loses its statistical significance after adjustment for 6MWD and FC, with a more pronounced increase of the P value after adjustment for the FC. The correlation between FC and hyponatremia despite being significant ($P < 0.001$) is weak ($r = -0.136$), not supporting collinearity as a relevant factor that could have affected our model. The reason why FC is the co-variable that most prominently neglects the association between hyponatremia and one-year mortality is not entirely clear.

In the REVEAL risk score, FC, but not hyponatremia, had a prognostic value and thus was included in the REVEAL risk score.[20] Based on the REVEAL registry, patients with PAH have a one-year survival rate of 85%, while the seven-year survival rate is only 49%. Based on the same registry, the HR for one-year mortality in PAH patients increased from 0.42 to 3.13 with PAH progression to a higher FC.[4] Thus, adjustment for FC helps stratify PAH patients based on their survival rate from the time of PAH diagnosis, an effect that may explain the observed loss in predicting mortality in patients with non-severe hyponatremia (sodium $= 131$–137 mmol/L).

The prognostic value of hyponatremia in PH patients had been previously investigated. The largest available study to date ($n = 635$) was done retrospectively and included patients with all groups of PH (i.e. not just WHO group 1 PH).[15] In this earlier study, the diagnosis of PH was based on the echocardiographic findings since only 69 patients underwent a RHC. Campo et al.[18] and Forfia et al.[14] prospectively followed patients with PAH diagnosed by RHC and demonstrated a direct and strong association between hyponatremia (defined by the investigators as serum sodium ≤ 136 mEq/L) and mortality; however, both studies were performed in relatively small cohorts of patients.

Hyponatremia has also been shown to be a predictor of poor outcomes in congenital heart disease.[21] Similarly, low serum sodium had been shown to correlate with higher rates of mortality in patients with PAH hospitalized with acute right heart failure in a prospective study of 46 patients[16] and another larger study of 119 patients.[17] Because of the relatively small sample size of these PAH cohorts, there are limitations in the number of variables that can be entered into the multivariable model. In fact, FC does not seem to have been included in either of the aforementioned studies in their multivariable models.

In the two largest studies available to date as mentioned above by Campo et al. ($n = 90$)[18] and Haddad et al. ($n = 119$),[17] which showed a positive association between hyponatremia and poor prognosis, based on the etiology of PAH, patients with CTD-PAH comprised the largest subgroup. Patient characteristics of our two cohorts differed and mostly consisted of patients with PAH due to idiopathic PAH and larger proportion with congenital heart disease-associated PAH. Hence, subgroup analyses were performed, which did not show significant association between non-severe hyponatremia and mortality in patients with CTD-PAH; however, the relatively small sample size of this subgroup of PAH patients (though larger than previous such reports) limits the significance of such an absence of a statistical association.

Our study has multiple implications. First, it is the largest study available to date to show that only severe hyponatremia (sodium ≤ 130 mmol/L) may carry a prognostic value in PAH in a multi-variable regression model. Due to the small number of patients with severe degree of hyponatremia, further studies on this population of patients are warranted. However, based on the results of this study, it becomes evident that non-severe hyponatremia, with sodium levels ≥ 131 mmol/L, has no significant independent prognostic value in the assessment of one-year mortality in patients with PAH. This finding differs from previously reported studies. Second, this study highlights the importance of functional status for multivariable models in future investigations designed to assess PAH patient mortality and survival, and the pathophysiologic basis for such an interaction should be further elucidated.

Hyponatremia has been established as a strong predictor of a poor prognosis in left-sided heart failure.[6,7] Patients with heart failure and hyponatremia have a different pathophysiology characterized by excessive vasopressin release and activation of the sympathetic nervous system and the RAAS.[22] While the exact cut-off point for sodium indicating significant change in the pathophysiologic mechanisms is still to be determined, significant correlation of severe hyponatremia (sodium ≤ 130 mmol/L) and poor survival in patients with heart failure has been shown.[8] The same authors showed significant association of hyponatremia and high plasma renin activity, suggesting that low serum sodium can be used as an indirect marker of the RAAS activation.[23] Despite multiple large studies on the role of hyponatremia as a prognostic factor in patients with heart failure, it is still unclear whether its treatment significantly improves patient survival.[24–27] Trials in PAH targeting the RAAS system are ongoing.[28]

Hyponatremia has also been shown to be an independent predictor of mortality in patients with cirrhosis and ascites and significantly improved prediction of the waitlist mortality after its addition to the MELD score.[10–12] Borroni et al. showed that in-hospital mortality was significantly higher in the subgroup of patients with cirrhosis who had serum sodium < 125 mmol/L.[13] Heuman et al. showed that the highest rate of mortality was observed among cirrhotic patients with persistent ascites who also had severe hyponatremia < 130 mmol/q/L.[12] Biggins et al. demonstrated a strong association between serum sodium < 126 mmol/L at listing for liver transplant or while listed and mortality rate among patients with cirrhosis.[11]

Limitations

This analysis is limited by the secondary analysis study design and small sample size of patients with severe hyponatremia. However, this is the largest study available to date to evaluate the role of hyponatremia in predicting patient survival in PAH. It is also limited by the inability to adjust for all variables that may affect sodium level, including, for example, the inability to adjust for the use of loop diuretics or other diuretics including potassium-sparing diuretics (such as aldosterone), whether at baseline or during the follow-up period.

Conclusions

Non-severe hyponatremia (sodium level of ≥ 131 mmol/L) is associated with one-year mortality but it loses its significance when adjusted for 6MWD and FC in the multivariable regression model, with a more pronounced loss of statistical significance after adjustment for the FC. Severe hyponatremia (sodium ≤ 130 mmol/L) is strongly associated with one-year mortality in patients with PAH even after adjustment for other co-variables.

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References

1. Tuder RM, Archer SL, Dorfmuller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25 Suppl): D4–12.

2. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25 Suppl): D42–50.

3. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25 Suppl): D34–41.

4. Benza RL, Miller DP, Barst RJ, et al. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest* 2012; 142(2): 448–456.

5. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* 2012; 141(2): 354–362.

6. Kusaka H, Sugiyama S, Yamamoto E, et al. Low-normal serum sodium and heart failure-related events in patients with heart failure with preserved left ventricular ejection fraction. *Circ J* 2016; 80(2): 411–417.

7. Klein L, O'Connor CM, Leimberger JD, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 2005; 111(19): 2454–2460.

8. Lee WH and Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986; 73(2): 257–267.

9. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, et al. Hyponatremia is an independent predictor of adverse clinical outcomes in hospitalized patients due to worsening heart failure. *J Cardiol* 2014; 63(3): 182–188.

10. Ruf AE, Kremers WK, Chavez LL, et al. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl* 2005; 11(3): 336–343.

11. Biggins SW, Rodriguez HJ, Bacchetti P, et al. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology* 2005; 41(1): 32–39.

12. Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004; 40(4): 802–810.

13. Borroni G, Maggi A, Sangiovanni A, et al. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. *Dig Liver Dis* 2000; 32(7): 605–610.

14. Forfia PR, Mathai SC, Fisher MR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008; 177(12): 1364–1369.

15. Rabinovitz A, Raiszadeh F and Zolty R. Association of hyponatremia and outcomes in pulmonary hypertension. *J Card Fail* 2013; 19(8): 550–556.

16. Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 35(6): 1286–1293.

17. Haddad F, Peterson T, Fuh E, et al. Characteristics and outcome after hospitalization for acute right heart failure in patients with pulmonary arterial hypertension. *Circ Heart Fail* 2011; 4(6): 692–699.

18. Campo A, Mathai SC, Le Pavec J, et al. Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension. *Eur Respir J* 2011; 38(2): 359–367.

19. Fares WH, Bellumkonda L, Tonelli AR, et al. Right atrial pressure/pulmonary artery wedge pressure ratio: A more specific predictor of survival in pulmonary arterial hypertension. *J Heart Lung Transplant* 2016; 35(6): 760–767.

20. Sitbon O, Benza RL, Badesch DB, et al. Validation of two predictive models for survival in pulmonary arterial hypertension. *Eur Respir J* 2015; 46(1): 152–164.

21. Dimopoulos K, Diller GP, Petraco R, et al. Hyponatraemia: A strong predictor of mortality in adults with congenital heart disease. *Eur Heart J* 2010; 31(5): 595–601.

22. Farmakis D, Filippatos G, Parissis J, et al. Hyponatremia in heart failure. *Heart Fail Rev* 2009; 14(2): 59–63.

23. Dzau VJ, Packer M, Lilly LS, et al. Prostaglandins in severe congestive heart failure. Relation to activation of the renin–angiotensin system and hyponatremia. *N Engl J Med* 1984; 310(6): 347–352.

24. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007; 297(12): 1319–1331.

25. Gheorghiade M, Gottlieb SS, Udelson JE, et al. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol* 2006; 97(7): 1064–1067.

26. Gheorghiade M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007; 297(12): 1332–1343.

27. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004; 291(16): 1963–1971.

28. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/results?cond=Pulmonary+Hypertension&term=spironolactone&cntry1=&state1=&SearchAll=Search+all+studies&recrs= (accessed 8 April 2017).