ORIGINAL ARTICLE

Hyponatremia and 30 days mortality of patients with acute pulmonary embolism

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Background: Hyponatremia has poor outcomes in other cardiopulmonary disorders, but its predictive value in predicting mortality of patients with acute pulmonary embolism is unknown. So, we evaluate the mortality of inpatients diagnosed with pulmonary embolism (PE) who had hyponatremia at the time of admission. **Materials and Methods:** By conducting a cohort study in patients with acute pulmonary embolism admitted in Al-Zahra Hospital during the 24 months of the date of March 2012 to March 2014. We evaluated 224 patients admitted with a primary diagnosis of PE. We used logistic regression analysis to evaluate the independent relation among serum sodium levels at the time of presentation and 30 days mortality, with severity of illness and other patient risk factors were adjusted. **Results:** 109 patients (48.7%) had normal sodium level (serum level >137 mmol/L). 115 patients had sodium level bellow 137 mmol/L. Of these, 56 (25%) had a sodium level 135-137 mmol/L and 59 (26.3%) had a sodium level <135 mmol/L. Patients with a serum sodium of >137, 135-137, and <135 mmol/L had a cumulative 30-day mortality of 14%, 21%, and 42% ($P < 0.0001$), respectively. The mortality of patients with lower serum sodium was significantly increased. When the pulmonary embolism severity index and also its simplified form were replaced in the model and while some confounding variables such patients with a history of cancer, chronic pulmonary disease, heart failure, and chronic renal failure were excluded from statistics, the findings still remained similar. **Conclusion:** Among patients presenting with PE, hyponatremia is common and is an independent risk factor that increasing short-term mortality. This result could be encountered as a variable in determining of PE severity and mortality.

Key words: Hyponatremia, mortality, prognosis, pulmonary embolism, pulmonary embolism severity index

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INTRODUCTION

Acute pulmonary embolism (PE) is the third common cardiovascular causes of hospital admission and mortality, following stroke, and acute coronary syndrome. Predictors of mortality following acute PE include: Simultaneous malignancy, chronic pulmonary disease, age older than 70 years, systemic hypotension at time of admission, heart failure, right ventricular akynesia and dysfunction, and biomarkers such as B-type natriuretic peptide and cardiac troponins.[1-3]

Among hospitalized patients, hyponatremia is a common electrolyte abnormality, and recent data showed that it had associated with poor outcome in patients with acute and chronic cardiovascular and pulmonary diseases, like heart failure, acute myocardial infarction and parenchymal lung infection. Besides in patients with cirrhosis and ascites while waiting for a liver transplant, hyponatremia is a great predictor of death.[1,2,4]

Our purpose was to evaluate the association between hyponatremia following admission and 1-month mortality of patients with acute PE. If found, this routinely available low cost laboratory finding, may be used in determining prognostic indexes of patients with acute PE.

MATERIALS AND METHODS

This is a cohort single center study conducted in a Tertiary Referral Medical Hospital in Center of Iran from March 2012 to March 2014.

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Study patients

252 consecutive patients with confirmed diagnosis of PE admitted our hospital were included in this study and prospectively followed. The final outcome and prognosis were evaluated during the course of hospitalization and within 30 days of initial presentation.

Inclusion criteria

Evidence of PE should be documented by either computed assisted tomography pulmonary angiography or by ventilation/perfusion pulmonary scintigraphy besides clinical and investigational evidence in favor of the diagnosis in the absence of an alternative one.

Exclusion criteria

Patients who were not definitively diagnosed as having PE were excluded from this study.

Definition of hyponatremia and outcomes

The hyponatremia was defined in our study as a baseline serum sodium level 137 mmol/L or lower. Sodium level between 135 and 137 was considered mild hyponatremia and amounts of sodium bellow 135 had severe hyponatremia.[3]

Our study outcome was pulmonary emboli related mortality within 30 days of initial presentation.

Clinical and demographic variables

At time of patients arrival in our hospital with suspicious to PE, a detailed medical history was obtained through a standardized questionnaire containing specific questions about symptoms, presence of known risk factors such as: Use of hormone replacement therapy, pregnancy or oral contraceptives, concomitant malignancy, recent trauma or surgery within the last 4 weeks, complete bed rest for >3 days, concurrent diseases, and medication use. In addition, variables such as hemoptysis prior to medication, altered menal status, New York Heart Association class, mode, and duration of predominant symptoms such as, chest pain, abdominal pain, fatigue, palpitations, dizziness, syncope, orthopnea, cough, and cyanosis at presentation and overt right ventricular failure prior the onset of symptoms and clinical signs included mean systolic blood pressure (SBP) and diastolic blood pressure, shock index (heart rate/SBP), hypoxemia, and evidence of deep venous thrombosis were considered. Severity of the PE was evaluated by PE severity index (PESI), a confirmed prognostic model for patients with PE.[5-8] We also used the simplified PESI (sPESI) format,[9] which are included: History of malignancy, chronic cardiopulmonary disease, age >80 years, pulse >110 beats/min, SBP <100 mmHg, and SpO_2 <90%.

Statistical analyses

In order to compare baseline characteristics for patient discharges across three levels of serum sodium (<135, 135-137, and >137 mmol/L), we applied Kruskal-Wallis test for contiguous variables and Chi-square test for categorical variables. We used the log-rank test and survival analyses to compare the cumulative 1-month mortality by sodium level, and stratified our evaluations of mortality by plasma sodium level and original PESI severity and its sPESI subclasses.

In order to evaluate the relation between plasma sodium level and mortality, we also used logistic regression analysis with adjusting for patient severity of illness by using all PESI severity models.

Ethics

The study method was approved by the Isfahan University Medical Ethics Review Committee, and all participants consciously signed a written consent. In this scheme, any intervention by the research team could not be applied and patients were treated under view of healthcare team and according to the protocol in the emergency department of the hospital.

RESULTS

Two hundred fifty-two patients with confirmed diagnosis of PE (59% men, median age of 56 years, and mean age 59 years ranging from 19 to 95 years) were evaluated. We excluded 16 (6.5%) patients for missed next their follow-up, 6 (2.4%) patients refused to participate to this study, and 6 (2.4%) patients were died not correlated to PE or its side effect. The study cohort included 224 patient admitted with a diagnosis of acute PE from Alzahra University Hospitals; 109 patients (48.7%) had normal sodium level (serum level >137 mmol/L). 115 patients had sodium level below 137 mmol/L. Of these, 56 (25%) had a sodium level 135-137 mmol/L, and 59 (26.3%) had a sodium level below 135 mmol/L. Primary patient characteristics by level of serum sodium are noted in Table 1.

Association between plasma sodium level and 1 month mortality

Overall, 53 of 224 patients (23.6%) died at the end of 30 days. As shown in Figure 1, patients with a serum sodium level of >137, 135-137, and <135 mmol/L had a cumulative 1-month mortality of 14%, 21%, and 42% ($P < 0.0001$), respectively.

After adjustment of patient for severity of PE by PESI risk class, mortality was also significantly higher in patients with lower serum sodium level [Table 2].

When the sPESI risk class was evaluated, the 30-day mortality remained significantly increased for patients with sodium level lower than 135 mmol/L [Table 3, Figure 2]. In order to omitted the role of some confounding variables

Table 1: Primary patient characteristics by level of serum sodium

Variables	All patients (*n* = 224)	Serum sodium level (mmol/L)			*P*
		<135 (*n* = 59)	135-137 (*n* = 56)	>137 (*n* = 109)	
Demographic					
Age, mean year, (SD)	57 (19)	61 (17)	56 (20)	55 (18)	>0.05
Male sex (%)	132 (59)	37 (63)	24 (43)	46 (42)	
Age >65 years (%)	83 (42)	27 (48)	23 (41)	42 (39)	
Comorbid diseases					
History of cancer	39 (17.5)	15 (25)	10 (18)	14 (13)	>0.05
COPD	50 (22)	12 (20)	9 (16)	29 (27)	
Heart failure	23 (10)	7 (13)	8 (14)	8 (7)	
CKD	6 (2.5)	2 (3.6)	1 (1.8)	3 (2.8)	
Physical examination findings					
Pulse >110 per min	88 (40)	29 (50)	25 (45)	34 (31)	>0.05
Systolic BP <100 mmHg	46 (20)	12 (20)	15 (27)	19 (17)	
Respiratory rate >30 per min	42 (19)	9 (15)	12 (22)	21 (19)	
Altered mental status	20 (9)	13 (22)	3 (5.5)	4 (3.7)	
Arterial oxygen saturation <90%	66 (30)	14 (24)	16 (28)	36 (33)	
Laboratory parameters					
Blood glucose >200 mg/dl	37 (16.5)	12 (20)	10 (18)	15 (14)	>0.05
Creatinin >1.5 mg/dl	12 (5.5)	5 (8.5)	1 (1.8)	6 (5.5)	
PESI risk class					
I	34 (15)	6 (10)	6 (11)	22 (20)	<0.007
II	40 (18)	8 (14)	12 (21)	20 (18)	
III	47 (21)	8 (14)	14 (26)	25 (23)	
IV	49 (22)	11 (18)	12 (21)	26 (24)	
V	54 (24)	26 (44)	12 (21)	16 (15)	
PESI risk class					
Low risk	74 (33)	14 (24)	18 (32)	42 (39)	<0.05
High risk	150 (67)	45 (76)	38 (68)	67 (61)	
Hospitalized ward					
General, pulmonary	134 (60)	33 (56)	28 (50)	73 (67)	>0.05
Emergency, ICU	3 (1)	1 (1)	2 (3.5)	0	
Surgery	22 (10)	7 (12)	6 (10.5)	9 (8)	
Other medical	65 (29)	18 (31)	20 (36)	27 (25)	

SD = Standard deviation; COPD = Chronic obstructive pulmonary disease; CKD = Chronic kidney disease; ICU = Intensive Care Unit; PESI = Pulmonary embolism severity index

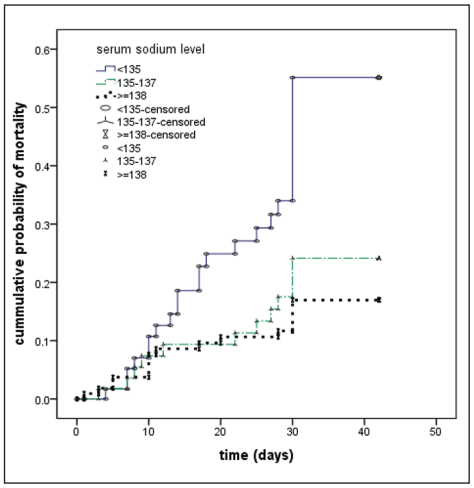

Figure 1: Kaplan-Meier estimates of cumulative 30-day mortality for patients with pulmonary embolism by baseline level of serum sodium

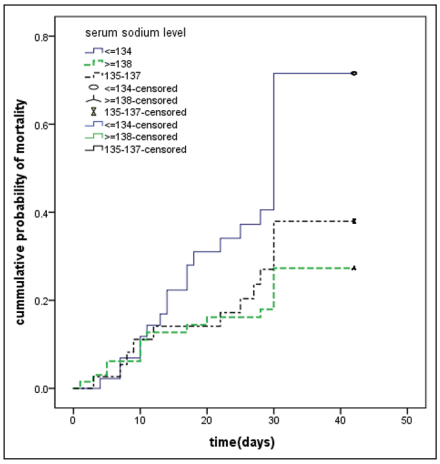

Figure 2: Kaplan-Meier estimates of 30-day mortality and level of serum sodium stratified by severity of illness in high risk patients (high score pulmonary embolism severity index) ($P < 0.05$)

such as history of cancer, heart failure, renal failure, or chronic obstructive pulmonary disease, all of them were excluded from analysis, but the mortality was still significantly different [Figure 3].

Table 2: Mortality and level of serum sodium stratified by severity of illness (PESI)

PESI risk class	Serum sodium level (mmol/L)			*P*
	<135 (mmol/L) (*n* = 59)	135-137 (mmol/L) (*n* = 56)	>137 (mmol/L) (*n* = 109)	
I	1 (4)	0	0	<0.007
II	1 (4)	0	1 (6)	
III	2 (8)	2 (7)	2 (12)	
IV	4 (16)	3 (25)	5 (42)	
V	17 (68)	7 (58)	8 (50)	
Total (%)	25/59 (42)	12/56 (21)	16/109 (14)	

PESI = Pulmonary embolism severity index

Table 3: Level of serum sodium and 30 days mortality stratified by severity of illness

Simplified PESI score	Serum sodium			Total
	<135 (mmol/L)	135-137 (mmol/L)	>137 (mmol/L)	
Low score	2 (14)	0 (18)	1 (42)	3 (74)
High score	23 (45)	12 (38)	15 (67)	50 (150)
Total	25 (59)	12 (56)	16 (109)	

Simplified PESI. Number in parenthesis indicates total number of patients in each groups. PESI = Pulmonary embolism severity index

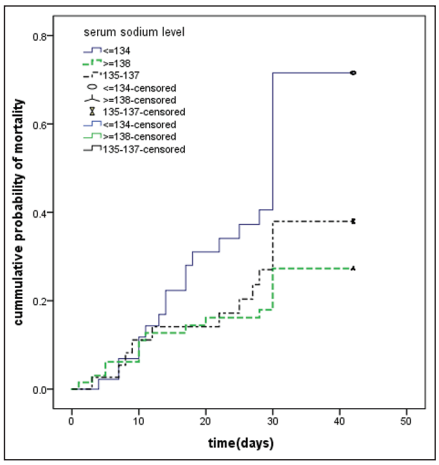

Figure 3: Kaplan-Meier estimates of 30-day mortality by level of serum sodium in patients with pulmonary embolism without chronic heart failure, chronic obstructive pulmonary disease, chronic renal failure, and cancer, the cumulative mortality was 56.2, 25, and 18.8% for patients with a sodium level. <135, 135-137, and, ≥138 mmol/l (*P* < 0.002)

DISCUSSION

According to our results, a significant proportion of patients with PE (26.3%) is hyponatremic (serum sodium <135 mmol/L) at the time of presentation. Serum sodium <135 mmol/L was observed in only approximately 2% of the community subjects, but associated with a 3.5-fold increased incidence of adverse outcome.[5] Among the patients with PE and hyponatremia, had significant higher 30-days mortality than patients without hyponatremia (42% for sodium level below 135 mmol/L vs. 14% for sodium level more than 137 mmol/L). So, severity of hyponatremia could increase mortality.

Our findings show that the mortality of patients with high PESI score and low sodium level was about 3 times over normonatremic (serum sodium >137 mmol/L) group. So, it seems that we could be able to use sodium level as a prognostic factor in patients with PE. There are no another papers about using this factor in determination of mortality in these patients.

With exclusion of some confounding variables such as: Chronic lung disease, previous history of cancer, renal failure, or heart failure the results remained similar. So, hyponatremia adversely affects outcomes across the all subclasses in severity of illness (PESI risk classes I-V), even with exclusion of the lower-risk patients (low PESI score), the mortality was significantly increased. In addition, some studies show that mild hyponatremia in the general population associated with increased mortality.[6,7] According to these it seems that hyponatremia is an independent predictor of short-term mortality in PE.

Hyponatremia can be an indicator of severity of disorders, which may be predictive of however not causally related to mortality. In the patients with cardiovascular disease, hyponatremia may suggestive of significant physiologic abnormalities (e.g., low effective circulating volume with consequent disturbances of renal filtration rate and distal sodium delivery, raised levels of arginine vasopressin, or neurohormonal activation).[4] Hyponatremia is a significant indicator of heart failure severity with poor prognosis.[5,8,9] Besides, in patients with cirrhosis and ascites while waiting for a liver transplant, hyponatremia is a great predictor of death. Adding hyponatremia to the model for end-stage liver disease (MELD) score is a better predictor of death than the MELD score alone, especially in patients with low MELD scores. Interestingly, correction of hyponatremia in these patients may not improve prognosis after liver transplantation.

In order to explain increased 1-month mortality among the PE patients with hyponatremia, we first point to relation between hyponatremia and sympathetic nerves hyper activity. In patients with left ventricular dysfunction, hyponatremia is an indicator of neurohormonal activation. It might cause release of vasopressin leading to hyperactivity of the sympathetic and renin-angiotensin aldosterone system axis.[1] Neurohormonal activation was also seen in patients with pulmonary arterial hypertension and right ventricular dysfunction.[1,10] So, as showed in two previous studies, in the setting of PE-related pulmonary arterial hypertension with right heart dysfunction, hyponatremia may initiated the neurohormonal activation, and finally resulted in increased mortality of patients with PE.[11,12]

Chronic inflammation may lead to production of interleukin-6 at inflammatory lesions, which can stimulate an excessive secretion of antidiuretic hormone resulting

in hypochloremia and hyponatremia.[5] Despite all these, recent hyponatremia treatment guidelines stated that "hyponatremia remains incompletely understood because of its association with a plethora of underlying disease states, and its multiple etiologies with differing pathophysiologic mechanisms."[13]

Some studies about chronic heart failure show that correction of hyponatremia by use of vasopressin antagonists does not improve outcome in general,[5] but other studies had different consequences.[8,14] Similar findings about pulmonary embolism are not available and prospective studies are necessary to determine whether correcting of hyponatremia improves outcomes or not.

Finally, more information is needed for using of serum sodium levels along with other known items of severity, in determining the prognosis of patients with pulmonary embolism.

Study limitations

1. Due to referrals role of our hospital, a measure of actual samples of selected patients may not accessible, and this may cause increase mortality of patients in this study compared to other studies.
2. In our patients, serum sodium levels after discharge were not checked. So, the role of persistent hyponatremia vs. temporary hyponatremia cannot be evaluated.
3. In this study, the role of hyponatremia correction and modalities of PE treatment on prognosis are not assessed.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

SKh and FF conducted and edited the manuscript. BT designed and analyzed and interpreted data. All authors read and approved the final manuscript.

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