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Prognostic Importance of Hyponatremia in Patients with Acute Pulmonary Embolism

THESE

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par

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Prognostic importance of Hyponatremia in patients with acute pulmonary embolism

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Rapport de synthèse

Enjeux et contexte: L'hyponatrémie est un trouble électrolytique fréquent et associé à un pronostic défavorable dans de nombreuses affections cardiovasculaires (1-5), pour lesquelles il est un marqueur de l'activation neurohumorale (6). Sa valeur pronostique chez les patients se présentant avec une embolie pulmonaire était jusque là inconnue ; elle fait l'objet de la présente étude.

Objectifs: Examiner chez les patients hospitalisés pour une embolie pulmonaire, les associations entre hyponatrémie et mortalité ainsi qu'avec le taux de réhospitalisation.

Méthodes: Nous avons étudié les données de 13'728 patients avec un diagnostic principal d'embolie pulmonaire provenant de 185 hôpitaux en Pennsylvanie (janvier 2000 à novembre 2002.) Nous avons utilisé un modèle de régression logistique afin d'établir l'association indépendante entre le niveau de sodium lors de la présentation aux urgences et la mortalité ainsi que le taux de réhospitalisation durant 30 jours. Nous avons ajusté pour les caractéristiques du patient (race, assurance, sévérité de la maladie, usage de la thrombolyse) et de l'hôpital (région, taille, avec ou sans médecins en formation.)

Résultats principaux: Une hyponatrémie (sodium ≤ 135 mmol/l) était présente chez 2907 patients (21.1%). Les patients avec un sodium >135, 130-135, et <130 mmol/l avaient une mortalité cumulée à 30 jours de 8.0%, 13.6%, et 28.5% (*P* <0.001), et un taux de réadmission de 11.8%, 15.6%, et 19.3% (*P* <0.001), respectivement. Comparés aux patients avec un sodium >135 mmol/l, les odd ratios ajustés concernant la mortalité étaient significativement plus important pour les patients avec un sodium compris entre 130 et 135 mmol/l (OR 1.53, 95% CI: 1.33-1.76) ou <130 mmol/l (OR 3.26, 95% CI: 2.48-4.29). Les odd ratios ajustés concernant la réhospitalisation étaient également augmentés pour les patients présentant un sodium entre 130 et 135 mmol/l (OR 1.28, 95% CI: 1.12-1.46) ou <130 mmol/l (OR 1.44, 95% CI: 1.02-2.02).

Conclusions et perspectives: L'hyponatrémie est fréquente chez les patients se présentant avec une embolie pulmonaire, de plus elle est un prédicateur indépendant de la mortalité à court terme, ainsi que du taux de réhospitalisation. La natrémie est une information généralement disponible lors de l'établissement d'un pronostic. Bien que cette association soit compatible avec une activation neurohumorale, nous ne pouvons pas attester des mécanismes impliqués, du fait que notre étude ne donne pas d'informations sur d'autres étapes de la physiologie de cette association.

Prognostic Importance of Hyponatremia in Patients with Acute Pulmonary Embolism

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At a Glance Commentary:

Scientific knowledge on the subject: Although associated with adverse outcomes in left ventricular heart failure, pneumonia, and pulmonary hypertension, the prognostic value of hyponatremia, a marker of neurohormonal activation, in patients with acute pulmonary embolism is unknown.

What this study adds to the field: In patients with acute pulmonary embolism, hyponatremia at presentation is common and is associated with a higher risk of 30-day mortality and readmission. Hyponatremia may serve as an easy-to-use marker to identify patients with pulmonary embolism who are at high-risk of adverse outcomes. Future studies should examine whether hyponatremia reflects neurohormonal activation and right ventricular dysfunction.

ABSTRACT

Rationale: Although associated with adverse outcomes in other cardiopulmonary conditions, the prognostic value of hyponatremia, a marker of neurohormonal activation, in patients with acute pulmonary embolism is unknown.

Objectives: To examine the associations between hyponatremia and mortality and hospital readmission rates for patients hospitalized with pulmonary embolism.

Methods: We evaluated 13,728 patient discharges with a primary diagnosis of pulmonary embolism from 185 hospitals in Pennsylvania (01/2000-11/2002). We used random-intercept logistic regression to assess the independent association between serum sodium levels at the time of presentation and mortality and hospital readmission within 30 days, adjusting for patient (race, insurance, severity of illness, use of thrombolytic therapy) and hospital factors (region, size, teaching status).

Measurements and Main Results: Hyponatremia (sodium ≤ 135 mmol/l) was present in 2907 patients (21.1%). Patients with a sodium level >135, 130-135, and <130 mmol/l had a cumulative 30-day mortality of 8.0%, 13.6%, and 28.5% (*P* <0.001), and a readmission rate of 11.8%, 15.6%, and 19.3% (*P* <0.001), respectively. Compared to patients with a sodium >135 mmol/l, the adjusted odds of dying were significantly greater for patients with a sodium 130-135 mmol/l (OR 1.53, 95% CI: 1.33-1.76) and a sodium <130 mmol/l (OR 3.26, 95% CI: 2.48-4.29). The adjusted odds of readmission were also increased for patients with a sodium 130-135 mmol/l (OR 1.28, 95% CI: 1.12-1.46) and a sodium <130 mmol/l (OR 1.44, 95% CI: 1.02-2.02).

Conclusions: Hyponatremia is common in patients presenting with pulmonary embolism and is an independent predictor of short-term mortality and hospital readmission.

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INTRODUCTION

Hyponatremia is a common electrolyte abnormality among hospitalized patients and is associated with poor outcomes in patients with acute and chronic cardiopulmonary diseases, such as left ventricular heart failure, acute myocardial infarction, and pneumonia (1-5). In patients with left ventricular heart failure, hyponatremia is strongly correlated with plasma neurohormone concentrations (e.g., norepinephrine, renin, and angiotensin II) all of which predict adverse outcomes (6). Neurohormone-mediated release of vasopression is responsible for the decrease in serum sodium in these patients (6).

A more recent study demonstrated that hyponatremia was also associated with right ventricular dysfunction and poor survival in patients with pulmonary arterial hypertension (7). In this study, the authors suggested that hyponatremia may result from neurohormonal activation and be a consequence of more advanced right ventricular dysfunction (7).

Acute pulmonary embolism (PE) is a major health problem; in 2005, 140,000 patients were discharged with a primary diagnosis of PE from U.S. hospitals (8), with an estimated average 30-day mortality of 9% (9). Early death following PE is strongly associated with right ventricular dysfunction (10). Based on a previously observed association between abnormal sodium levels and mortality in patients with PE (9), we hypothesized that a low serum sodium at baseline, a marker of neurohormonal activation, may indicate a worse prognosis in patients with this illness.

Our goal was to examine the association between hyponatremia and 30-day mortality and hospital readmission using a large, statewide sample of patients with acute PE. If found, such association may be useful to risk-stratify patients with acute PE, given

that serum sodium is a low-cost, routinely available laboratory parameter. Some of the results of this study have been previously reported in the form of an abstract (11).

METHODS

Patient Identification and Eligibility

We identified all patients with PE discharged from non-governmental acute care hospitals in Pennsylvania (01/01/2000-11/30/2002) using the Pennsylvania Health Care Cost Containment Council (PHC4) database (9). We included inpatients aged ≥ 18 years who were discharged with a primary International Classification of Diseases, 9th Clinical Modification diagnosis of PE or a secondary diagnosis for PE and one of the following primary diagnoses that represent complications or treatments of PE: respiratory failure, cardiogenic shock, cardiac arrest, secondary pulmonary hypertension, syncope, thrombolysis, and intubation/mechanical ventilation. A detailed methodological description is available in the online supplement.

Patient and Hospital Characteristics

Patient demographic characteristics and insurance status were abstracted from the PHC4 database (9). Baseline clinical and laboratory parameters were obtained by linking eligible patients to the MediQual Atlas database (9). We quantified severity of illness using the Pulmonary Embolism Severity Index (PESI), a validated prognostic model for patients with PE (9). The PESI comprises 11 routinely available clinical predictor variables. A total point score for a given patient is obtained by

summing the points for each applicable predictor. Based on the total score, each patient is classified into one of five severity classes (I-V), with 30-day mortality ranging from 1.1% to 24.5%. We ascertained the hospital characteristics from the PHC4 database and from the Council of Teaching Hospitals of the Association of American Medical Colleges.

Definition of Hyponatremia and Outcomes

We defined hyponatremia as a baseline serum sodium level ≤ 135 mmol/l. While no commonly accepted cut-point exist for defining hyponatremia, most recent cardiopulmonary studies used a serum sodium level ≤ 134-136 mmol/l to define the threshold (2, 7, 12).

Our primary study outcome was all-cause mortality within 30 days of presentation based on the National Death Index (13). To ascertain our secondary outcome, hospital readmission for any reason to any acute care hospital in Pennsylvania within 30 days, we used the PHC4 database.

Statistical Analyses

To compare baseline characteristics for patient discharges across three levels of serum sodium (< 130, 130 to 135, > 135 mmol/l), we performed chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. We used survival analyses and the log-rank test to compare the cumulative 30-day mortality and hospital readmission rates by sodium level. We also stratified our comparisons of mortality by sodium level and the five PESI severity classes.

We used multivariable logistic regression to examine the independent association between sodium level and mortality, after adjusting for patient race, insurance, severity of illness using PESI severity class, thrombolytic therapy, and hospital region, size and teaching status. To account for patient clustering within hospital, we used random-intercept logistic regression with the two levels defined by patient and hospital site. We used the same logistic model to examine the association between sodium level and readmission in patients discharged alive. We also examined whether the addition of serum sodium increases the prognostic performance of the PESI using net reclassification and integrated discrimination improvement (14).

RESULTS

Of the 17,733 patient discharges that met our inclusion criteria, we excluded 323 with only a secondary code indicative of PE (1.8%), 767 patient transfers from another hospital (4.3%), 265 subsequent transfers to another hospital (1.5%), 777 discharges without a match to key clinical findings (4.4%), 70 without a linkage to the National Death Index (0.4%), and 1803 (10.2%) with an undocumented serum sodium at the time of presentation. The study cohort comprised 13,728 patient discharges with a diagnosis of PE from 185 Pennsylvania hospitals; 2907 (21.1%) had hyponatremia (serum level ≤ 135 mmol/l). Of these, 2598 (18.9%) had a sodium level 130 to 135 mmol/l and 309 (2.2%) had a sodium level < 130 mmol/l. Compared to the 13,728 enrolled patients, the 1803 excluded because of an undocumented serum sodium were significantly younger (median age, 64 vs 67 years; P <0.001) and were less likely to have a history of heart failure (10.7% vs 16.5%; P <0.001) and chronic lung disease (14.7% vs 18.9%; P

<0.001). Compared to eligible patients with a serum sodium documented, these 1803 excluded patients were also less likely to have a pulse ≥ 110/minute (11.1% vs 18.5%; *P* <0.001), a systolic blood pressure < 100 mm Hg (7.8% vs 10.8%; *P* <0.001), a respiratory rate ≥ 30/minute (8.3% vs 15.4%; *P* <0.001), a body temperature < 36°C (14.4% vs 16.9%; *P* =0.007), an altered mental status (5.9% vs 7.5%; *P* =0.02), and an arterial oxygen saturation < 90% (3.9% vs 8.5%; *P* <0.001) at presentation.

Comparison of Baseline Patient Characteristics by Serum Sodium Level

As shown in Table 1, patients admitted with lower serum sodium were older, more likely to have comorbid diseases (cancer, chronic lung disease, heart failure) and more likely to have signs of clinical severity (tachycardia, hypotension, tachypnea, hypothermia, altered mental status, hypothermia, and hypoxemia). Consequently, there were a higher proportion of patients in PESI risk classes IV and V among patients with lower serum sodium. Patients with lower serum sodium were also significantly more likely to have hyperglycemia and elevated serum creatinine.

Association of Serum Sodium Level and 30-Day Mortality

Overall, 1308 of 13,728 patients (9.5%) died at 30 days. As shown in Figure 1, patients with a serum sodium > 135, 130 to 135, < 130 mmol/l had a cumulative 30-day mortality of 8.0%, 13.6%, and 28.5% (*P* <0.001), respectively. Mortality in these three groups diverged day 1 after admission and the difference continued to increase over the 30-day follow-up. Mortality was also significantly increased among patients with lower serum sodium stratified by each of the five PESI risk classes at presentation (Table 2).

After adjustment for patient race, insurance, severity of illness using PESI risk class, administration of thrombolytic therapy, hospital region, and hospital size and teaching status (Table 3), the odds of 30-day mortality remained significantly increased for patients with a sodium level 130 to 135 mmol/l (odds ratio [OR] 1.53, 95% confidence interval [CI]: 1.33-1.76) and a sodium level < 130 mmol/l (OR 3.26, 95% CI: 2.48-4.29). When the PESI risk class was replaced in the model with the 11 variables comprising the PESI and laboratory parameters (serum glucose > 250 mg/dl, serum creatinine > 1.5 mg/dl, and serum troponin ≥ 0.1 ng/ml) or when the 5951 patients with a history of cancer, chronic lung disease, or heart failure were excluded from analysis, the results remained similar.

Patient reclassifications for 30-day mortality are summarized in Table 4. For 38 of 1308 patients (2.9%) who died within 30 days of admission, classification improved using serum sodium level in addition to the PESI. Conversely, 154 of 12,420 patients (1.2%) who were alive within 30 days of admission were reclassified up. The net reclassification improvement was estimated at 1.7% (P <0.001), corresponding to a modest but statistically significant improvement. The integrated discrimination improvement was also statistically significant (0.009; P <0.001).

Association of Serum Sodium Level and 30-Day Readmission

The 30-day readmission rate was estimated in 12,762 patients, after the exclusion of 840 patients who died in the hospital, 91 who were still hospitalized at 30 days after admission, and 35 with unknown readmission status. Of these, 1596 (12.5%) were readmitted within 30 days. As shown in Figure 2, patients with a sodium level > 135, 130 to 135, and < 130 mmol/l had a cumulative 30-day readmission rate of 11.8%,

15.6%, and 19.3% (P <0.001), respectively. After adjustment (Table 3), patients with a sodium level 130 to 135 mmol/l (OR 1.28, 95% CI: 1.12-1.46) and a sodium level < 130 mmol/l (OR 1.44, 95% CI: 1.02-2.02) had significantly increased odds of 30-day readmission. When the PESI risk class was replaced in the model with the 11 variables comprising the PESI and laboratory parameters (serum glucose > 250 mg/dl, serum creatinine > 1.5 mg/dl, and serum troponin ≥ 0.1 ng/ml) or when the 5951 patients with a history of cancer, chronic lung disease, or heart failure were excluded from analysis, the results were unchanged.

DISCUSSION

Our results demonstrate that a substantial proportion of patients with PE (21.1%) are hyponatremic at the time of presentation. After adjusting for potential patient- and hospital-related confounders and the administration of thrombolytic therapy, we found that patients with hyponatremia had a significantly higher 30-day mortality than patients without hyponatremia and that the mortality rate increased with the severity of hyponatremia. The higher mortality among patients with hyponatremia was observed across all PESI risk classes. Similarly, we also observed a significant association between hyponatremia and 30-day hospital readmission. To our knowledge, our study represents the first to demonstrate the prognostic importance of hyponatremia in patients with PE.

Several explanations are possible for the association between hyponatremia and increased 30-day mortality in patients with PE. Hyponatremia is a well-known marker of neurohormonal activation in patients with left ventricular heart failure and reflects

nonosmotic release of vasopressin consequent to activation of the sympathetic and renin-angiotensin-aldosterone system axis (6, 15). Neurohormonal activation has also been demonstrated in patients with pulmonary arterial hypertension, and occurs in proportion to the degree of right ventricular dysfunction (16, 17). Therefore, hyponatremia may indicate neurohormonal activation in the context of PE-related pulmonary arterial hypertension and subsequent right heart dysfunction, a known factor of adverse prognosis in patients with PE (10). Indeed, a prior prospective study of patients with chronic pulmonary arterial hypertension demonstrated a strong association between hyponatremia and the presence of right ventricular dysfunction and short-term survival (7). Future prospective studies should examine whether hyponatremia reflects neurohormonal activation and right ventricular dysfunction in patients with acute PE.

Another explanation for the observed association between hyponatremia and adverse outcomes may be the presence of unmeasured prognostic factors that are unrelated to right ventricular dysfunction. In a recent study of middle-aged and elderly community subjects without a history of heart failure, hyponatremia was an independent predictor of death, regardless of concomitant diuretic use, renal and hepatic disease, and hyperglycemia (18). In large retrospective and prospective cohort studies, hyponatremia also significantly increased short-term mortality in unselected inpatients (19-22). Indeed, the relationship between hyponatremia and adverse outcomes is incompletely understood because of its association with a multitude of underlying disease states, and its multiple causes with different pathophysiologic mechanisms (23).

Our study also shows that after adjustment for patient and hospital characteristics and the administration of thrombolytic therapy, hyponatremia in the acute phase of PE is an independent predictor for future hospital admissions, reinforcing the prognostic

importance of a low serum sodium level. Our findings are consistent with the results from prior studies that found significantly higher hospital readmission rates in hyponatremic patients with acute myocardial infarction and heart failure (2, 12, 24).

Our findings have both clinical and research implications. Clinically, patients with PE who are hyponatremic at presentation, carry a higher risk of short-term mortality and hospital readmission and may therefore potentially benefit from more intensive surveillance in the hospital and after discharge. Further research is warranted to determine whether correction of hyponatremia (e.g., with vasopressin receptor antagonists or other treatments) is associated with improved outcomes for patients with PE. Evidence suggests that patients with left ventricular heart failure who have persistent hyponatremia have a significantly higher risk of short-term mortality or hospitalization for heart failure than patients in whom hyponatremia was corrected (24). Similarly, resolution of admission hyponatremia during hospitalization appears to attenuate the increased mortality risk conferred by hyponatremia among unselected inpatients (21).

Our work has several potential limitations. First, patients in the study sample were identified by use of ICD-9-CM codes for PE rather than standardized radiographic criteria, and patient eligibility may therefore be subject to study selection biases due to hospital coding procedures. In prior studies, up to 96% of patients with specific codes for PE had objectively documented disease on the basis of chart review criteria (25-27). Second, our sample excluded 10.2% of younger, healthier, and less severely ill patients in whom serum sodium was not measured at the time of admission. However, because hyponatremia adversely affects outcomes across the full spectrum of severity of illness (PESI risk classes I-V), the exclusion of these lower risk patients is unlikely to change

our study results. Third, because measures of right ventricular function and neurohormonal activation were not available in our database, we could not examine whether these factors are linked to the pathophysiology of hyponatremia. Moreover, we had no information about diuretic use and hypervolemic hyponatremic states such as cirrhosis or nephrotic syndrome. Thus, we could not explore whether these conditions are associated with the higher observed mortality among patients with hyponatremia. Fourth, because we had no information on sodium levels after hospital discharge, the prognostic implications of transient versus persistent hyponatremia could not be analyzed. Finally, we can only detect associations, not causality from these data. Thus, we cannot determine whether hyponatremia has a specific effect on the pathophysiology of PE or if it is simply a marker of adverse outcome.

In conclusion, in this large sample of patients hospitalized with acute PE, hyponatremia at presentation was common and was associated with a higher risk of 30-day mortality and readmission. Hyponatremia may serve as an easy-to-use marker to identify patients with PE who are at high-risk of adverse medical outcomes. Future studies should examine whether hyponatremia reflects neurohormonal activation and right ventricular dysfunction in patients with acute PE and whether correction of this electrolyte abnormality is associated with improved patient outcomes.

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Figure Legend 1

Cumulative Mortality by Level of Serum Sodium

Kaplan-Meier estimates of 30-day mortality for patients with pulmonary embolism by baseline level of serum sodium. The cumulative mortality was 8.0%, 13.6%, and 28.5% for patients with a sodium level > 135, 130 to 135, and < 130 mmol/l (P <0.001), respectively.

Figure Legend 2

Cumulative Readmission Rate by Level of Serum Sodium

Kaplan-Meier estimates of 30-day readmission rate for patients with pulmonary embolism by baseline level of serum sodium. The cumulative readmission rate was 11.8%, 15.6%, and 19.3% for patients with a sodium level > 135, 130 to 135, and < 130 mmol/l (P <0.001), respectively.

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Table 1. Baseline Patient Characteristics by Level of Serum Sodium

Characteristics	All patients (N=13,728)	Serum Sodium Level (mmol/l) <130 (N=309)	130 to 135 (N=2598)	>135 (N=10,821)	*P*-Value
	Number (%) or Median (IQR)				
Demographics					
Age, years	67 (52-77)	71 (59-79)	68 (55-78)	67 (52-77)	<0.001
Male gender	5525 (40.2)	122 (39.5)	1099 (42.3)	4304 (39.8)	0.06
Race					0.38
White	11166 (81.3)	249 (80.6)	2149 (82.7)	8768 (81.0)	
Black	1459 (10.6)	34 (11.0)	252 (9.7)	1173 (10.8)	
Other/unknown	1103 (8.0)	26 (8.4)	197 (7.6)	880 (8.1)	
Insurance status					<0.001
None/unspecified	197 (1.4)	1 (0.3)	37 (1.4)	159 (1.5)	
Government	7685 (56.0)	205 (66.3)	1513 (58.2)	5967 (55.1)	
Medicaid	1013 (7.4)	25 (8.1)	204 (7.8)	784 (7.2)	
Private	4833 (35.2)	78 (25.2)	844 (32.5)	3911 (36.1)	
Comorbid diseases					
History of cancer	2669 (19.4)	105 (34.0)	685 (26.4)	1879 (17.4)	<0.001
Chronic lung disease	2602 (18.9)	68 (22.0)	540 (20.8)	1994 (18.4)	0.009
Heart failure	2266 (16.5)	80 (25.9)	494 (19.0)	1692 (15.6)	<0.001

Continued

Table 1 Continued

Characteristics	All patients (N=13,728)	Serum Sodium Level (mmol/l) <130 (N=309)	130 to 135 (N=2598)	>135 (N=10,821)	*P*-Value
	Number (%) or Median (IQR)				
Physical examination findings					
Pulse ≥ 110 beats per minute	2542 (18.5)	87 (28.2)	596 (22.9)	1859 (17.2)	<0.001
Systolic blood pressure < 100 mm Hg	1484 (10.8)	65 (21.0)	417 (16.0)	1002 (9.3)	<0.001
Respiratory rate ≥ 30 breaths/minute	2111 (15.4)	69 (22.3)	446 (17.2)	1596 (14.7)	<0.001
Altered mental status*	1024 (7.5)	39 (12.6)	218 (8.4)	767 (7.1)	<0.001
Temperature < 36°C	2316 (16.9)	64 (20.7)	403 (15.5)	1849 (17.1)	0.03
Arterial oxygen saturation < 90%†	1165 (8.5)	30 (9.7)	250 (9.6)	885 (8.2)	0.04
Laboratory parameters					
Glucose > 250 mg/dl	1000 (7.3)	54 (17.5)	335 (12.9)	611 (5.6)	<0.001
Creatinine > 1.5 mg/dl	1809 (13.2)	67 (21.7)	412 (15.9)	1330 (12.3)	<0.001
Troponin ≥ 0.1 ng/ml	4497 (32.8)	106 (34.3)	817 (31.4)	3574 (33.0)	0.26
PESI risk class					<0.001
I	2531 (18.4)	12 (3.9)	334 (12.9)	2185 (20.2)	
II	2894 (21.1)	45 (14.6)	463 (17.8)	2386 (22.0)	
III	3018 (22.0)	65 (21.0)	578 (22.2)	2375 (21.9)	
IV	2253 (16.4)	70 (22.6)	512 (19.7)	1671 (15.4)	
V	3032 (22.1)	117 (37.9)	711 (27.4)	2204 (20.4)	

Continued

Table 1 Continued

Characteristics	All patients (N=13,728)	Serum Sodium Level (mmol/l) <130 (N=309)	130 to 135 (N=2598)	>135 (N=10,821)	*P*-Value
	Number (%) or Median (IQR)				
Thrombolysis	329 (2.4)	6 (1.9)	75 (2.9)	248 (2.3)	0.19
Types of hospitals attended					
Hospital region					<0.001
Pittsburgh and surrounding areas	3174 (23.1)	66 (21.4)	509 (19.6)	2599 (24.0)	
Northwest Pennsylvania	947 (6.9)	20 (6.5)	187 (7.2)	740 (6.8)	
Southern Laurel Highlands	713 (5.2)	11 (3.6)	124 (4.8)	578 (5.3)	
North central Pennsylvania	942 (6.9)	21 (6.8)	211 (8.1)	710 (6.6)	
South central Pennsylvania	2187 (15.9)	57 (18.4)	451 (17.4)	1679 (15.5)	
Northeast Pennsylvania	841 (6.1)	23 (7.4)	179 (6.9)	639 (5.9)	
Eastern Pennsylvania	1366 (9.9)	19 (6.1)	288 (11.1)	1059 (9.8)	
Surrounding Philadelphia	2037 (14.8)	36 (11.6)	314 (12.1)	1687 (15.6)	
Philadelphia	1521 (11.1)	56 (18.1)	335 (12.9)	1130 (10.4)	
Average annual volume of PE, quartiles					0.02
< 10	747 (5.4)	8 (2.6)	147 (5.7)	592 (5.5)	
10 to 20	1569 (11.4)	30 (9.7)	257 (9.9)	1282 (11.8)	
21 to 42	3517 (25.6)	87 (28.2)	686 (26.4)	2744 (25.4)	
> 42	7895 (57.5)	184 (59.5)	1508 (58.0)	6203 (57.3)	

Continued

Table 1 Continued

Characteristics	All patients (N=13,728)	Serum Sodium Level (mmol/l) <130 (N=309)	130 to 135 (N=2598)	>135 (N=10,821)	*P*-Value
	Number (%) or Median (IQR)				
Hospital size and teaching status					<0.001
Large nonteaching (≥ 350 beds)	2748 (20.0)	73 (23.6)	615 (23.7)	2060 (19.0)	
Small nonteaching (< 350 beds)	7542 (54.9)	149 (48.2)	1337 (51.4)	6056 (56.0)	
Teaching	3438 (25.1)	87 (28.2)	646 (24.9)	2705 (25.0)	

Abbreviations: IQR = interquartile range; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index.

*Defined as disorientation, lethargy, stupor, or coma.

†With or without supplemental oxygen.

Table 2. Association of Mortality and Level of Serum Sodium Stratified by Severity of Illness

	Serum Sodium Level (mmol/l)			
	<130	**130 to 135**	**>135**	***P*-Value**
	30-Day Mortality, n/N (%)			
PESI risk class				
I	0/12 (0.0)	10/334 (3.0)	22/2185 (1.0)	0.02
II	7/45 (15.6)	28/463 (6.0)	62/2386 (2.6)	<0.001
III	16/65 (24.6)	52/578 (9.0)	134/2375 (5.6)	<0.001
IV	15/70 (21.4)	73/512 (14.3)	156/1671 (9.3)	<0.001
V	50/117 (42.7)	190/711 (26.7)	493/2204 (22.4)	<0.001

Abbreviation: PESI = Pulmonary Embolism Severity Index.

Table 3. Association Between Level of Serum Sodium and Outcomes

Outcomes	Adjusted Odds Ratio*	95% Confidence Interval	*P*-Value
30-day all-cause mortality			<0.001
Serum sodium >135 mmol/l	1.00	-	
Serum sodium 130 to 135 mmol/l	1.53	1.33-1.76	
Serum sodium <130 mmol/l	3.26	2.48-4.29	
30-day hospital readmission rate†			<0.001
Serum sodium >135 mmol/l	1.00	-	
Serum sodium 130 to 135 mmol/l	1.28	1.12-1.46	
Serum sodium <130 mmol/l	1.44	1.02-2.02	

*The models were adjusted for patient race, insurance type, severity of illness using the Pulmonary Embolism Severity Index (including age, gender, history of cancer, chronic lung disease, or heart failure, systolic arterial blood pressure < 100 mm Hg, pulse ≥ 110/min., respiratory rate ≥ 30 breaths/min., body temperature < 36°C, arterial oxygen saturation < 90%, altered mental status), administration of thrombolysis, hospital region within Pennsylvania, and hospital size and teaching status. Adjusted odds ratios were estimated using random-intercept logistic regression with the two levels defined by patient and hospital site.

†Thirty-day readmission was estimated after the additional exclusion of 840 patients who died in the hospital, 91 who were still hospitalized 30 days after admission, and 35 with unknown readmission status, leaving a sample of 12,762 patients.

Table 4. Reclassification of Patients Who Died and Who Were Alive by 30 Days Based on the PESI With and Without Serum Sodium Level

PESI Without Serum Sodium Level	PESI With Serum Sodium Level (<130, 130 to 135, >135 mmol/l)					
Frequency	<2.3%	2.3-5.0%	5.1-8.8%	8.8-17.5%	>17.5%	Total
Patients who died by 30 days						
<2.3%	32	0	0	0	0	32
2.3-5.0%	0	90	0	7	0	97
5.1-8.8%	0	0	186	16	0	202
8.8-17.5%	0	0	0	229	15	244
>17.5%	0	0	0	0	733	733
Total	32	90	186	252	748	1308
Patients who were alive by 30 days						
<2.3%	2487	12	0	0	0	2499
2.3-5.0%	0	2759	0	38	0	2797
5.1-8.8%	0	0	2767	49	0	2816
8.8-17.5%	0	0	0	1954	55	2009
>17.5%	0	0	0	0	2299	2299
Total	2487	2771	2767	2041	2354	12420

Abbreviations: PESI = Pulmonary Embolism Severity Index

Figure 1

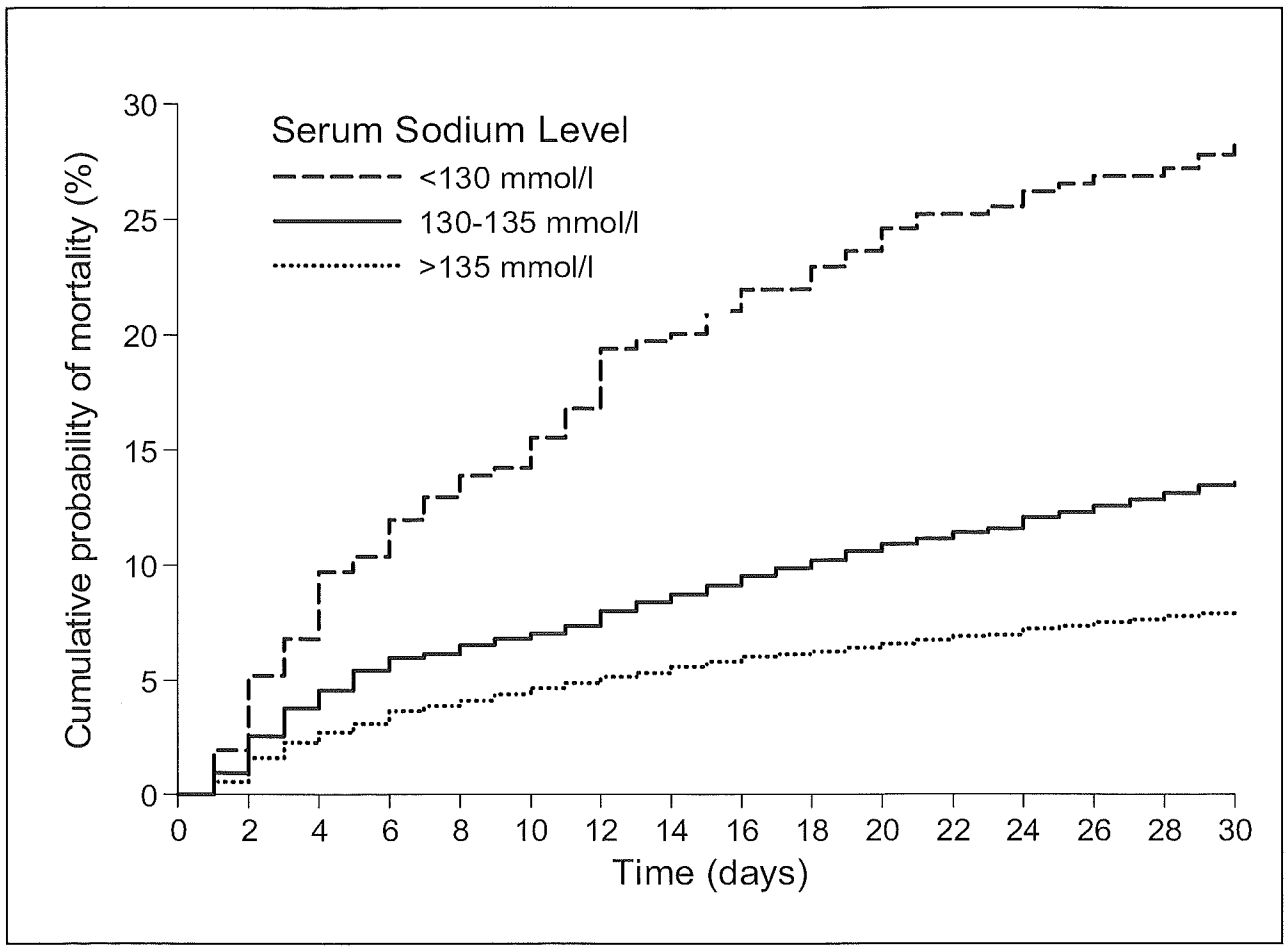
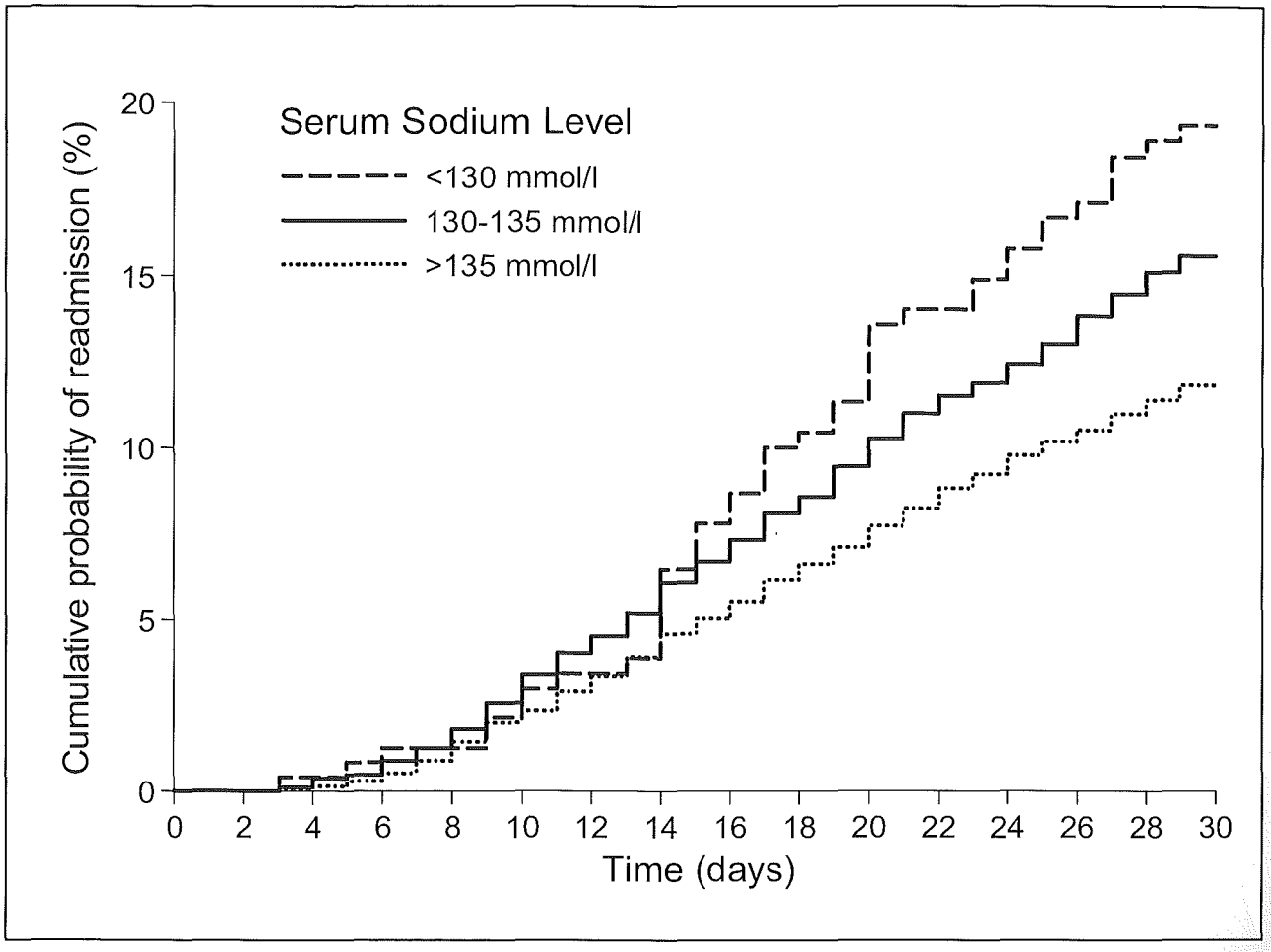

Serum Sodium Level
<130 mmol/l
130-135 mmol/l
>135 mmol/l
Cumulative probability of mortality (%)
0
5
10
15
20
25
30
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Time (days)

Figure 2


Serum Sodium Level
<130 mmol/l
130-135 mmol/l
>135 mmol/l
Cumulative probability of readmission (%)
0
5
10
15
20
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time (days)