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PROGNOSTIC VALUE OF HYPONATREMIA DURING ACUTE PAINFUL EPISODES IN SICKLE CELL DISEASE

Running Title: Hyponatremia in Sickle Cell Disease Acute Painful Episodes

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Abstract

Background. Low plasma sodium concentration has been recognized as a prognostic factor in several disorders but never evaluated in sickle cell disease. The present study evaluates its value at admission to predict a complication in adult sickle cell disease patients hospitalized for an initially uncomplicated acute painful episode.

Methods. The primary endpoint of this retrospective study, performed between 2010 and 2015 in a French referral center for sickle cell disease, was a composite criterion including acute chest syndrome, intensive care unit transfer, red blood cell transfusion or inpatient death. Analyses were adjusted for age, sex, hemoglobin genotype and concentration, LDH concentration, and white blood cell count.

Results. We included 1218 stays (406 patients). No inpatient death occurred during the study period. Hyponatremia (plasma sodium \leq 135 mmol/L) at admission in the center was associated with the primary endpoint (adjusted odds ratio (OR) 1.95 [95% confidence interval (CI) 1.3-2.91, $p=0.001$]), and with acute chest syndrome (OR 1.95 [95% CI 1.2-3.17, $p=0.008$]) and red blood cell transfusion (OR 2.71 [95% CI 1.58-4.65, $p<0.001$]), but not significantly with intensive care unit transfer (OR 1.83 [95% CI 0.94-3.79, $p=0.074$]). Adjusted mean length of stay was longer by 1.1 days (95% CI 0.5-1.6, $p<0.001$) in patients with hyponatremia at admission.

Conclusions. Hyponatremia at admission in the medical department for an acute painful episode is a strong and independent prognostic factor of unfavorable outcome, and notably acute chest syndrome. It could help targeting patients who may benefit from closer monitoring.

Keywords: sickle cell anemia; hyponatremia; pain; acute chest syndrome; prognosis

Introduction

Acute painful episodes, also called vaso-occlusive crises, are the most frequent acute manifestation of sickle cell disease¹. Their course is sometimes complicated by acute chest syndrome (the most frequent of these complications), pain resistant to strong opioids, organ damage, infection or thromboembolic events, and death. Acute chest syndrome and other acute complications require specific and urgent management, including antibiotics, red blood cell transfusion or transfer to the intensive care unit^{2,3}.

Early predictors of a complicated evolution during acute painful episodes could help clinicians individualize treatment and monitoring to prevent complications. Hyponatremia has been associated with the risk of death in unselected hospitalized patients⁴⁻⁶ and with poor outcome in various respiratory diseases⁷⁻¹⁰. Hyponatremia in respiratory diseases is usually due to an inappropriate secretion of antidiuretic hormone¹¹, which could also occur during acute painful episodes, especially in case of incipient or overt acute chest syndrome.

The aim of this retrospective observational study on routinely-collected health data was to evaluate the prognostic value of low plasma sodium concentration at admission in adult sickle cell disease patients hospitalized for an acute painful episode.

Patients and methods

This report complies with the RECORD statement¹². Detailed information regarding patients and methods is provided in the supplemental material.

Source of data

All but transfusion data were extracted from our institutional data warehouse storing routinely-collected health data. Transfusion data were obtained from the French blood products agency database.

Patients

All consecutive adult sickle cell disease patients hospitalized at least once for an acute painful episode in a referral center for adult sickle cell disease from January 2010 to April 2012 (first sample) or from April 2013 to June 2015 (second sample) were included. Hospitalizations were retrieved from the data warehouse using the International classification of diseases 10th revision diagnostic code D570, corresponding to a sickle cell acute painful episode.

All sickle cell disease genotypes were included and classified in two groups for analyses: one with the most severe genotypes (SS and S β^0) and the other one with the remaining genotypes (mostly SC and S β^+). We excluded stays with no diagnostic codes, and those already fulfilling the primary outcome criterion at admission (i.e. when acute chest syndrome, red blood cell transfusion or transfer intensive care unit occurred before admission in the center).

Laboratory data

We recorded plasma sodium concentration (normal range: 136-144 mmol/L) and laboratory variables already known to be associated with a complicated course in patients admitted for an acute painful episode^{13,14}: LDH and hemoglobin concentration, white blood cell count. We used the first laboratory values available within 48h following the admission or, if missing, in the 24h preceding admission in our center. If laboratory data was missing during this period or only recorded after outcome occurrence, it was imputed using multiple imputation methods¹⁵.

Outcomes

The primary outcome was a composite criterion including acute chest syndrome occurrence, intensive care unit transfer, red blood cell transfusion (either simple transfusion or exchange transfusion) or inpatient death. The secondary outcomes were each component of the composite criterion and total length of stay.

For billing purposes, acute chest syndrome is systematically coded as lower respiratory tract infection in our department, whether or not there is a proven infection. We therefore used international classification of diseases 10th revision codes J13 to J18 to retrieve acute chest syndromes in the data warehouse, then confirmed by one author (JSR) checking full medical records. In case of discordance between coding and manual checking, diagnosis was adjudicated after consensus with a second author (OS).

Acute chest syndrome was classified as definite when it associated acute fever and/or respiratory findings with a new infiltrate on chest imaging^{16–18} and probable when chest imaging was not performed but the patient had fever with chest rales motivating antibiotic treatment. Indications for transfusion and transfer in intensive care unit in our center adhere to the French guidelines for sickle cell disease management¹⁶, which are consistent with the American guidelines¹⁸.

Statistical analysis

We used two hospitalization samples from two disjoint time periods to check the consistency of our results as internal validation. We considered the findings were consistent if no significant heterogeneity (interaction $p < 0.1$) between samples was observed in the effect estimate of each predictor. We planned to pool the two samples for more precise estimates if they were consistent.

We used logistic and linear regression to evaluate the association between outcomes and plasma sodium concentration, adjusted for known or possible risk factors for poor outcome during acute painful episodes: age, sex, hemoglobin genotype and concentration, LDH concentration, white blood cell count. Plasma sodium concentration was first analyzed as a quantitative variable to assess the effect of the gradual decrease in plasma sodium concentration on outcomes. Standardized odds ratios (OR) were computed on z-scores to estimate and consistently compare the impact of a standard deviation change for each predictor. For more understandable effect estimates, we also computed the effect of hyponatremia (plasma sodium concentration ≤ 135 mmol/l).

We tested if plasma sodium concentration differed according to the time lag between hospitalization and measurement in patients who finally developed acute chest syndrome compared to those who did not. We also analyzed the association between outcomes and the change between the first available plasma sodium concentration and the last one before outcome occurrence.

We performed several sensitivity analyses. To address a possible bias due to multiple stays per patient, we used logistic regression limited to the first stay of each patient, weighted bootstrapping (attributing to each stay a weight of 1 divided by the number of stay for each respective patient) and within-cluster resampling (performing multiple iterations using datasets with only one stay per patient at each iteration). To account for unmeasured persistent confounding factors at the patient level, we used conditional logistic regression models with patients as strata.

Analyses were performed using the R environment for statistical computing¹⁹. We used interaction terms to test differences across samples and subgroups. We considered as significant $p \leq 0.1$ for interactions and $p \leq 0.05$ for all other analyses.

Ethics

French law does not require written patient consent for monocentric retrospective studies using patient data collected during routine care. Patients are informed and can freely opt out this process.

Results

Patients and stays

We included 580 stays (254 patients) in the first sample and 638 stays (245 patients) in the second sample, totaling 1218 stays (406 patients) in the pooled population. Reasons for exclusion are given in the flowchart (Figure 1). Acute chest syndrome was already present at admission in 142 potentially eligible stays (61% of all acute chest syndromes). The first and second samples shared 93 patients, accounting for 285 stays in the first sample and 350 stays in the second sample.

Patients had between 1 and 14 stays in the first sample, between 1 and 28 in the second sample and between 1 and 34 in the pooled sample. Age, sex and genotypes distribution were comparable in the two samples (Table S-1). Characteristics of patients and stays in the pooled population are reported in Table 1 according to the occurrence or not of the composite outcome. Numbers of outcome events in each sample are reported in Figure S1. Intensive care unit transfer was associated to acute chest syndrome in 75 % of cases (Figure S1).

Association between plasma sodium concentration and outcomes

Results of adjusted analyses in each sample are provided in Figure 2. The effect of all predictors on all outcomes was similar in the first and second sample and the following variables were associated with the composite outcome: plasma sodium concentration with an OR 1.47 [95% confidence interval (CI) 1.23 to 1.76; $p < 0.001$] for each 2.6 mmol/L decrease (one standard deviation of the sample distribution), LDH concentration OR 1.39 [95% CI 1.18 to 1.65; $p < 0.001$] for each 270 U/L increase, hemoglobin concentration OR 1.18 [95% CI 0.95 to 1.46; $p = 0.14$] for each 1.5 g/dL decrease and white blood cell count OR 1.26 [95% CI 1.04 to 1.52; $p = 0.016$] for each 4.4 G/L increase. Age, sex, and hemoglobin genotype were not associated with the primary outcome in unadjusted and adjusted analyses.

Plasma sodium concentration, as a quantitative variable, was the single variable significantly associated with all secondary outcomes in the pooled population. There was no significant interaction between the effects of plasma sodium concentration and age or hemoglobin genotype on any outcome. Further adjusting on acute chest syndrome incidence did not annulate, yet weakened, the association between natremia and red blood cell transfusion (OR 1.33 [95% CI 1.03 to 1.71; $p = 0.026$]) but nullified the association between natremia and intensive care unit transfer (OR 1.14 [0.82 to 1.60]; $p = 0.43$).

In adjusted analyses, hyponatremia (plasma sodium concentration ≤ 135 mmol/L) was associated with the primary outcome (OR 1.95 [95% CI 1.3 to 2.91; $p = 0.001$]), with acute chest syndrome (OR 1.95 [95% CI 1.2 to 3.17 $p = 0.008$]) and red blood cell transfusion (OR 2.71 [95% CI 1.58 to 4.65; $p < 0.001$]), but not significantly with intensive care unit transfer (OR 1.83 [95% CI 0.94 to 3.79; $p = 0.074$]). Adjusted length of stay was increased by 1.1 days [95% CI 0.5 to 1.6; $p < 0.001$] in case of hyponatremia.

Timing of plasma sodium concentration measurement and association with acute chest syndrome

Median time between admission and measurement of plasma sodium concentration was 1 [0-1] day in the pooled sample. Median time to diagnosis of acute chest syndrome from admission was 2 days [2-4]. Plasma sodium concentration was significantly lower when it was measured later in patients evolving to acute chest syndrome ($p = 0.098$ for the interaction between acute chest syndrome/no acute chest syndrome and the time lag between hospitalization and plasma sodium measurement). This interaction is shown in Figure S-2.

In the second sample, decrease of plasma sodium concentration between the first and the last available values before outcome was significantly associated with the composite criterion (OR 1.35 [95% CI 1.05 to 1.72; $p = 0.016$ for a decrease of one mmol/L/day]) and acute chest syndrome (OR 1.38 [95% CI 1.05 to 1.8 p

= 0.017]), but not with red blood cell transfusion ($p = 0.65$) or intensive care unit transfer ($p = 0.65$), as shown in Figure 3.

Recurrent stays analysis

Stratifying the model on each patient to limit confounding factors due to individual characteristics using conditional logistic regression and taking the over-representation of patients with multiple stays into account, using first stay analysis, weighted bootstrapping and within-cluster resampling, lead to similar estimates of the association of natremia and each outcome (Figure S-3).

Discussion

Summary of findings

Hyponatremia (plasma sodium concentration ≤ 135 mmol/L) at admission in the medicine department is strongly associated with complicated outcome, most notably acute chest syndrome, in sickle cell patients hospitalized for an initially uncomplicated acute painful episode. This association is independent from baseline demographic characteristics (age, sex, hemoglobin genotype) and from other prognostic factors ascertained by our study (lower hemoglobin concentration, higher white blood cell count and LDH concentration). There is a dose effect (OR of 1.47 [CI 95% 1.23-1.76]) for each 2.6 mmol decrease in plasma sodium concentration.

Strengths and limitations

The study is monocentric but uses internal validation through two disjoint samples of hospital stays with a time lag between them, intended to decrease the number of common patients, who nonetheless are 93/406 (22%).

Using diagnostic coding to retrieve acute chest syndrome exposes to classification errors, but coding for acute chest syndrome in our institution is standardized and all events were manually checked. Acute chest syndrome could already have been present before being recognized by the physicians in charge, as occurs in real life. In this case, hyponatremia could be a signal prompting earlier recognition.

Patients with recurrent stays could influence global results. We performed sensitivity analyses to address this risk of bias, using only the first stay for each patient, weighted bootstrapping and within-cluster resampling methods. All results were consistent.

We could not adjust our analyzes on the presence of spine or hip pain, a published predictor of adverse outcome during acute painful episodes¹³. However, our models were adjusted on many other published risk factors of adverse outcome during acute painful episodes^{13,14}: age, sex, hemoglobin genotype, white blood cell count, and hemoglobin and LDH concentrations. We did not evaluate several potential confounding factors, such as comorbidities, that could be associated both with a higher risk of complication during acute painful episodes and with hyponatremia. However, the impact of these persistent potential confounding factors is probably low since sensitivity analysis produced similar results when stratified at the patient level.

Intravenous hydration may have differed between patients and increased the risk of hyponatremia in some. However, hydration is standardized in our hospital from the admission in the emergency department to the medicine department: 2 liters of isotonic saline in the first 24h and 1 liter/24h thereafter.

Comparison with previous studies and interpretation

The composite criterion was defined to account for most severe complications of acute painful episodes, directly for acute chest syndrome and mortality, or indirectly through the need for a transfer to the intensive care unit and/or red blood cell transfusion for other complications. Acute chest syndrome was the most

frequent complication in our study. Consistent with a previously published study ²⁰, 61% of acute chest syndromes were already present at admission, therefore excluded from the study, and occurred on average 2 days after admission in the medical department when not initially present.

Consistent with previous studies, higher LDH concentration, higher white blood cell count and lower hemoglobin concentration were associated with the evolution to acute chest syndrome ^{13,14}. One of these studies developed a score including white blood cell and reticulocytes counts, hemoglobin concentration and pelvic or spine localization of pain to predict the evolution to acute chest syndrome ¹³. Its negative predictive value was excellent (99%), but its low positive predictive value (45%) leaves room for improvement, possibly by adding other predictors such as hyponatremia.

No other clinical study has evaluated the prognostic value of hyponatremia occurring during an acute painful event. Experimentally induced hyponatremia improves the deformability and adhesion of sickle red blood cells in vitro ²¹. However, the optimal plasma sodium concentration observed in this study (111 mmol/L) corresponds to life-threatening hyponatremia and is far from those observed in our study. Experimentally induced hyponatremia has been studied in sickle cell disease patients in the 80's ^{22,23}. However, due to discordant results and high risk of bias, no conclusion on the beneficial or deleterious effect of experimentally induced hyponatremia can be drawn from these studies and induced hyponatremia has not been used in clinical practice ever since.

The mechanism of observed hyponatremia in acute painful episode needs to be clarified. Acute chest syndrome was the most frequent outcome, and the association between hyponatremia and other outcomes was weakened (red blood cell transfusion) or nullified (intensive care unit transfer) after adjustment on acute chest syndrome occurrence. The main hypothesis is that hyponatremia could be due to an inappropriate secretion of anti-diuretic hormone associated with early subclinical lung damage that can evolve to acute chest syndrome. Although it has not been studied during acute chest syndrome, pulmonary disorders are a leading cause of inappropriate antidiuretic hormone secretion. In particular, hyponatremia is frequent at an early stage of pneumonia ^{11,24,25}, which may contribute to acute chest syndrome pathogenesis ^{20,26}. The fact that plasma sodium concentration was lower when it was measured later in patients who finally experience acute chest syndrome supports the hypothesis of an evolving lung injury leading to inappropriate secretion of anti-diuretic hormone and decreasing plasma sodium concentration over time, potentially favored by intravenous hydration.

Research and clinical perspectives

Our results need to be validated in cohorts from different centers, controlling for more potential confounding factors, like cardiovascular and pulmonary comorbidities or psychotropic drugs known to be associated with the syndrome of inappropriate antidiuretic hormone secretion. These studies, if prospective, should collect the data needed to explain the mechanism of hyponatremia during acute painful episode. Hyponatremia may lead to direct clinical consequences in the management of sickle cell disease patients. Indeed, a plasma sodium concentration ≤ 135 mmol/L at admission or a decreasing natremia over the first days of an acute painful episode could be regarded as early signs of incipient acute chest syndrome, prompting clinicians to closely monitor the clinical status of their patients. It could also be integrated in a scoring system to target a subgroup of patients that could benefit from preventive interventions such as incentive spirometry ^{27,28}, and a lower threshold for several treatments such as antibiotics or red blood cell transfusions ²⁹⁻³¹.

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J.-S.R., F.L. and O.S. designed the study. J.-S.R., C.B., S.B., G.G., F.L. and O.S. contributed to the production of initial data. O.J. and O.S. extracted data of the first sample from databases. J.-S.R., F.L. and O.S. manually verified and completed the data. K.Y. and O.S. extracted data of the second sample from the data warehouse. J.-S.R. and O. S. performed statistical analyses and wrote the manuscript. All authors interpreted the results, reviewed the manuscript and approved its final version.

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Conflict of interest disclosures

The authors declare no competing interest.

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None to declare.

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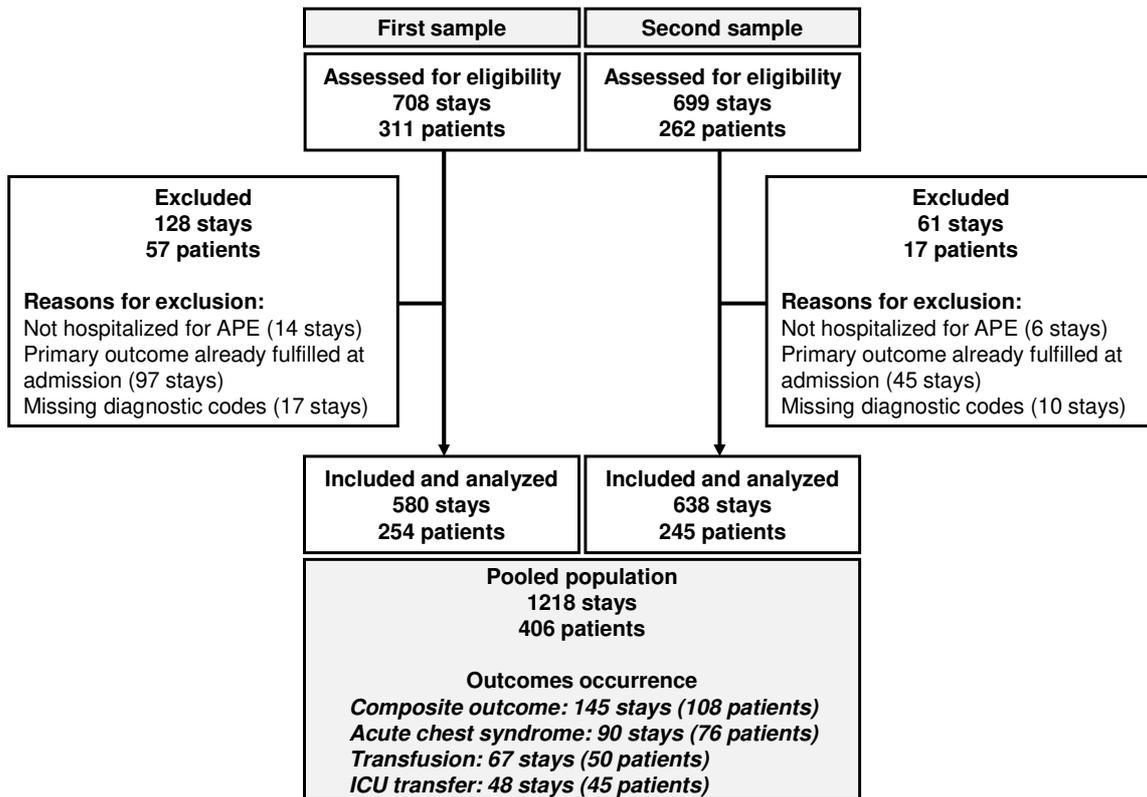
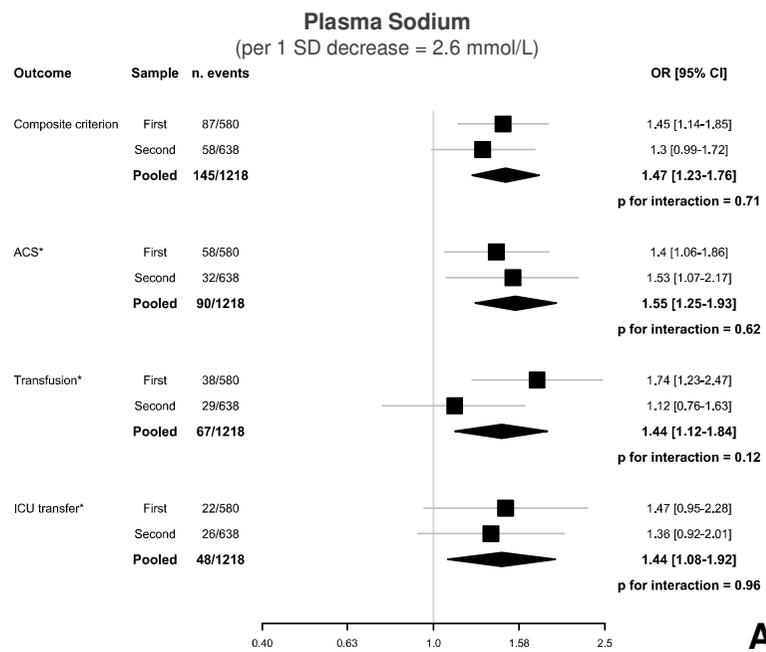
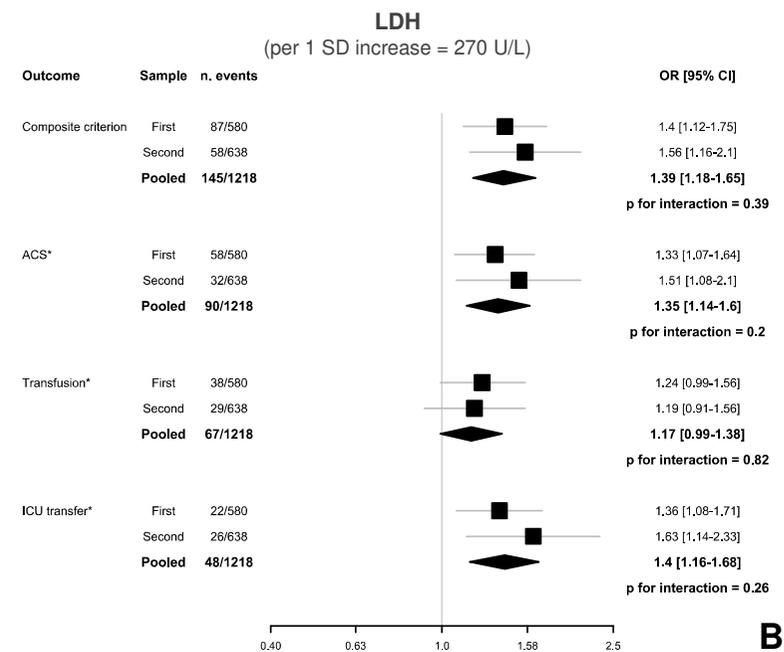


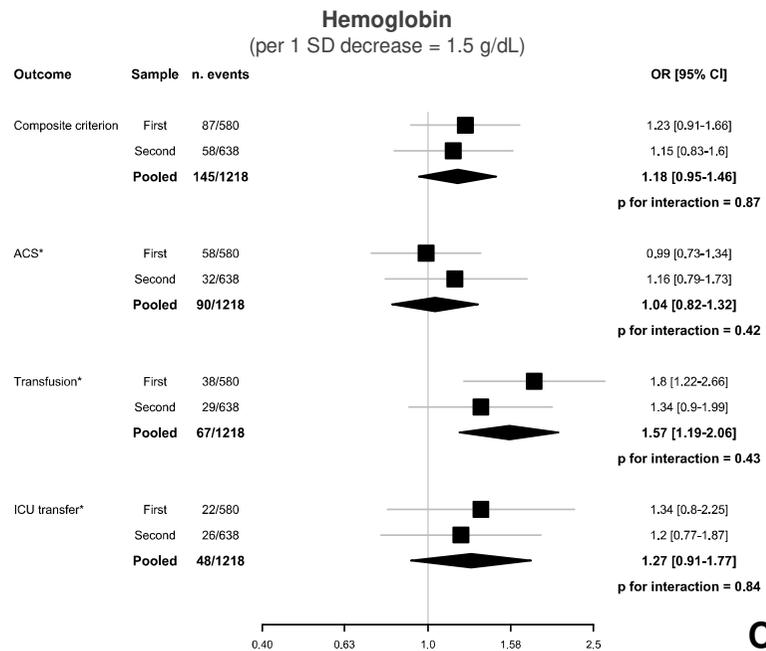
Figure 1. Selection flowchart of stays and patients. APE, acute painful episode; ICU, intensive care unit; RBC, red blood cell. If acute chest syndrome, red blood cell transfusion or a transfer in intensive care unit occurred before admission in the center, the primary outcome was considered as already fulfilled at admission and the stay was excluded from the analyzes.



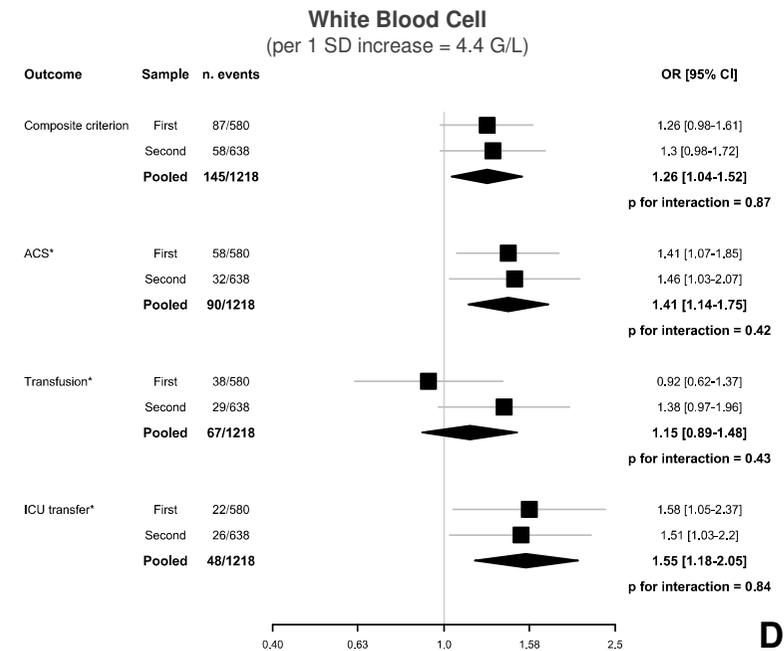
A



B



C



D

Figure 2. Adjusted analysis of the association between biological variables and outcomes. Logistic regression is adjusted for age, sex, hemoglobin genotype, white blood cell (WBC) count, lactate dehydrogenase (LDH) and hemoglobin concentration for the composite criterion, and on WBC count and LDH and hemoglobin concentration for other outcomes; odds ratio (OR) are normalized to one standard deviation increase for LDH (270 U/L) and WBC count (4.4 G/L), and to one standard deviation decrease for plasma sodium concentration (2.6 mmol/L) and hemoglobin concentration (1.5 g/dL). ACS, acute chest syndrome; ICU, intensive care unit; SD, standard deviation.

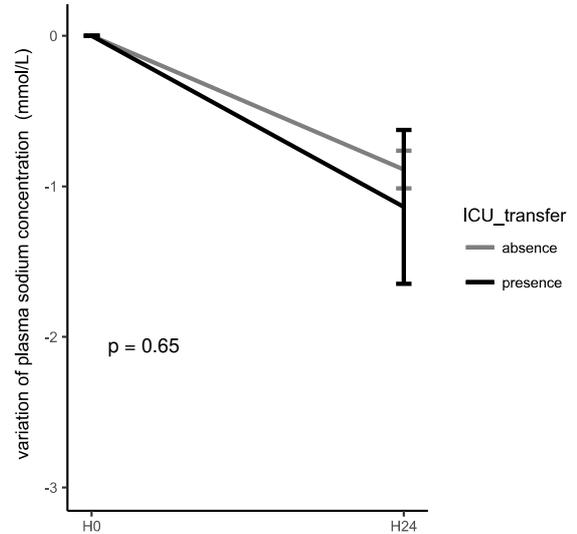
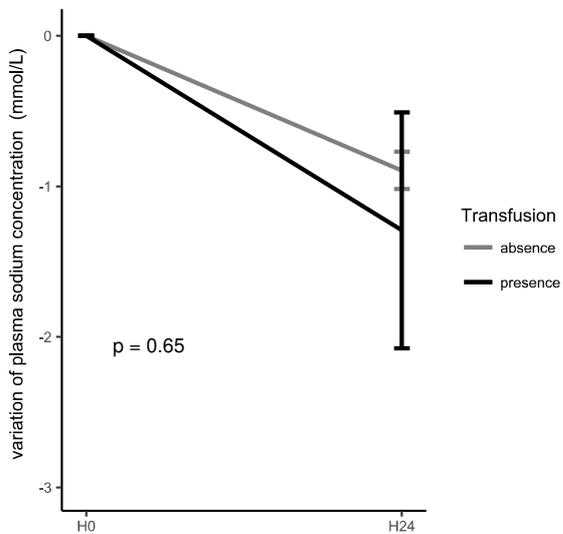
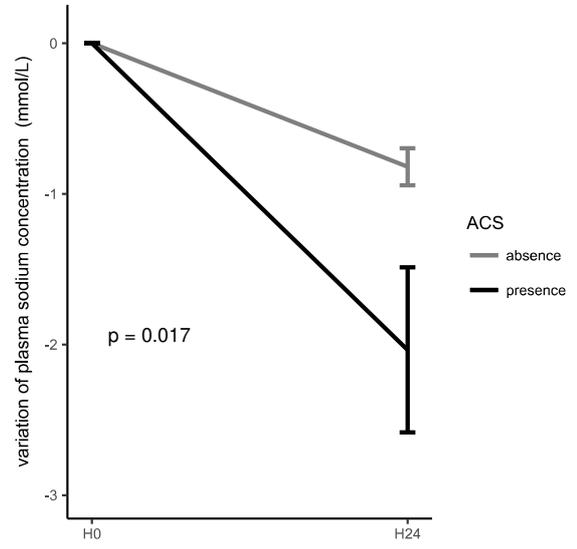
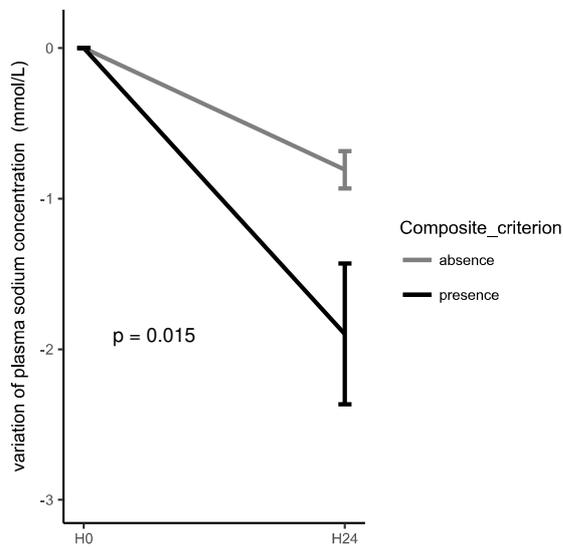


Figure 3. 24h decrease of plasma sodium concentration according to the occurrence or not of the different outcomes. ACS, acute chest syndrome; ICU, intensive care unit. H0 correspond to the time of first measurement of natremia during a stay, within 24h before admission.

Table 1. Characteristics of patients and stays according to the occurrence or not of the composite outcome in the pooled population.

	N (%) or median [Q1-Q3]			
	Missing Data	No composite outcome 1073 stays (378 patients [†])	With composite outcome 145 stays (108 patients [†])	Total 1218 stays (406 patients [†])
Patient data [†]				
Females	0 (0 %)	208 (55 %)	53 (49 %)	220 (54 %)
SS or Sβ ⁰ genotype [¶]	0 (0 %)	314 (83 %)	105 (97 %)	341 (84 %)
Age, years	0 (0 %)	26 [21-32]	26 [21-31]	26 [21-32]
Number of stays	0 (0 %)	2 [1-4]	3 [2-7]	2 [1-3]
Stay data				
Hospital stay duration, days	0 (0 %)	4 [3-7]	9 [6-11]	4 [3-7]
<i>Laboratory values at admission</i>				
Plasma sodium, mmol/L	75 (6 %)	138 [136-139]	136 [134-138]	138 [136-139]
LDH, U/L	159 (13 %)	416 [322-532]	519 [418-704]	425 [329-552]
Hemoglobin, g/dL	30 (2 %)	8.6 [7.7-9.6]	8.1 [7.3-9.3]	8.6 [7.6-9.6]
WBC count, G/L	30 (2 %)	11.2 [8.3-13.7]	12.6 [9.9-16.1]	11.2 [8.4-13.9]
<i>Timing of natremia measurement</i>				
day before admission	75 (6 %)	163 (16 %)	13 (10 %)	176 (15 %)
admission - day 1		700 (69 %)	98 (73 %)	798 (70 %)
day 2		147 (15 %)	22 (17 %)	169 (15 %)
<i>Outcome criteria</i>				
Acute chest syndrome	0 (0 %)		90 (62 %)*	90 (7 %)*
RBC transfusion	0 (0 %)		67 (46 %)	67 (6 %)
ICU transfer	0 (0 %)		48 (33 %)	48 (4 %)
Death	0 (0 %)		0 (0 %)	0 (0 %)

[†] 80 patients had stays with and without composite outcome; [¶] hemoglobin genotype distribution was: 309 patients SS, 5 Sβ⁰, 55 SC, 7 Sβ⁺, one SE and one SLepore in the group with no composite outcome, 102 patients SS, 3 Sβ⁰, 2 SC and one SLepore in the group with composite outcome, and 334 patients SS, 7 Sβ⁰, 56 SC, 7 Sβ⁺, one SE and one SLepore in the pooled population; * 16 were probable acute chest syndromes; N (%), number of patients or stays (percentage); [Q1-Q3], [first quartile-third quartile]; ICU, intensive care unit; LDH, lactate dehydrogenase (upper limit of the normal range for LDH: 250 U/L); RBC, red blood cell; WBC, white blood cell.