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Original article

Hypernatremia and moderate-to-severe hyponatremia are independent predictors of mortality in septic patients at emergency department presentation: A sub-group analysis of the need-speed trial

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ABSTRACT

Study objective: Early risk stratification of septic patients presenting to the emergency department (ED) is challenging. The aim of the study was to evaluate the prognostic role of plasmatic sodium level ($_pNa^+$) derangements at ED presentation in septic patients.

Methods: According to $_pNa^+$ at ED presentation patients were divided in eunatremic (136–145 mEq/L), hypernatremic (>145 mEq/L) and hyponatremic (<136 mEq/L). Hyponatremic patients were subsequently divided in mild (130–135 mEq/L), moderate (125–129 mEq/L) and severe (<125 mEq/L). 7 and 30-day mortality was evaluated according to $_pNa^+$ derangements and the degree of hyponatremia. The same analysis was then performed only in respiratory tract infection-related (RTI-r) sepsis patients.

Results: 879 septic patients were included in this analysis, 40.3% had hyponatremia, 5.7% hypernatremia. Hypernatremia showed higher mortality rates at both endpoints compared to eunatremia and hyponatremia ($p < 0.0001$ for both). Eunatremia and mild hyponatremia were compared *vs.* moderate-to-severe hyponatremia showing a significant difference in terms of 7 and 30-day survival ($p = 0.004$ and $p = 0.007$, respectively). The Cox proportional model identified as independent predictors of 7 and 30-day mortality moderate-to-severe hyponatremia (HR 4.89[2.38–10.03] and 1.79[1.07–3.01], respectively) and hypernatremia (HR 3.52[1.58–7.82] and 2.14[1.17–3.92], respectively). The same analysis was performed in patients with respiratory tract infection-related sepsis ($n = 549$), with similar results.

Conclusion: Both hypernatremia and moderate-to-severe hyponatremia at ED presentation independently predict mortality in septic patients, allowing early risk stratification and suggesting more aggressive therapeutic strategies.

1. Introduction

Early risk stratification of septic patients admitted to the Emergency Department (ED) is challenging [1,2] since signs and symptoms may be similar for patients who will have either a favorable or an adverse outcome. Among the strategies to detect patients at higher risk, some propose the clinical evaluation of tissue perfusion [3,4], whereas other focus on early signs of circulatory failure [5,6]. Again, the increase in many serum biomarkers levels, such as lactate, could alert to the need for aggressive resuscitative management. However most of these biomarkers have been studied and validated in later phases of sepsis and septic shock, notably in the intensive care unit (ICU) [7–10], so that their peculiar role in the ED, where they are rarely available, has been investigated only by few [11–13]. Moreover, predictive scores, such as APACHE 2 and SOFA, have been studied and validated in large multicentric studies, but the data needed to their computation are not always

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available during the initial evaluation performed in the ED while the qSOFA score, based only on readily available clinical data, seems to be influenced by comorbidities [2].

On the other hand, routine tests performed at ED presentation, such as blood and urine samples, may provide useful information to detect patients who need a more aggressive treatment [14,15]. In this regard, plasmatic sodium derangements, notably hypo- and hypernatremia, have been shown to worsen the prognosis of patients with cardiovascular, hepatic and respiratory diseases, as well as in ICU patients [16–20]. Nevertheless, few studies have evaluated the prognostic role of sodium abnormalities at ED admission, specifically on septic patients, in terms of mortality.

The aim of the present study is to evaluate whether plasma sodium concentration ($_{P}Na^{+}$) at ED admission can represent a reliable, cheap, quick and worldwide available predictor of mortality in patients with sepsis. The study derives from a subgroup analysis of the Need-Speed trial [12].

2. Materials and methods

2.1. Patients and aims

The aim and inclusion criteria of the Need-Speed trial have been previously published [12]. Briefly, in this multicenter observational trial, consecutive adult patients admitted to the EDs of five Italian hospitals between March 2013 and March 2015, were enrolled if they met two or more criteria of systemic inflammatory response syndrome (SIRS) [21].

The aim of this subgroup analysis was to evaluate the prognostic role of sodium derangements in patients with sepsis, in terms of prediction of 7 and 30-day mortality. We, included in this analysis only patients who had been classified as “septic” according to the Sepsis-2 criteria [21]. Subsequently, we performed the same analysis on patients with respiratory tract infection-related (RTI-r) sepsis.

2.2. Data collection

The study was approved by the Ethical Committee of each of the participating centers. At the time of inclusion, patients were informed of the study protocol and possibility was given to them to refuse participation. If clinical conditions were too serious to obtain an informed consent, the patients’ next of kin were informed of the study protocol and possibility was given to them to refuse the participation for their relatives. Subsequently, if the clinical condition had improved and if the patients were able to consent, we informed them about the study, and possibility was given to them to refuse to participate. In such a case, their data were not entered into analysis.

At the time of enrolment demographic, hemodynamic and respiratory data were collected, together with the Glasgow Coma Scale (GCS). At the same time, arterial and peripheral venous blood samples were drawn, respectively for blood gas analysis and for cellular blood count and biochemical assays, as well as for blood culture. In addition, urine samples were collected, and patients underwent a chest X-ray, according to the clinical judgement of the treating physician.

Patients who presented clinical, radiological or microbiological findings that suggested respiratory tract infection as the primary cause for sepsis were included in the RTI-r sepsis subgroup.

2.3. Sodium concentration

Among the data collected in the Need-Speed database, $_{P}Na^{+}$ at the time of ED presentation was recorded. Patients were first divided according to the presence or absence of sodium abnormalities (dysnatremic *vs.* non-dysnatremic, respectively) and then three different subgroups were created:

- ü Eunatremia: $136 \leq {}_{P}Na^{+} \leq 145$ mEq/L;
- ü Hyponatremia: $_{P}Na^{+} < 136$ mEq/L;
- ü Hypernatremia: $_{P}Na^{+} > 145$ mEq/L.

Subsequently, hyponatremic patients [22] were further divided into:

- ü Mild hyponatremia: $130 \leq {}_{P}Na^{+} \leq 135$ mEq/L;
- ü Moderate hyponatremia: $125 \leq {}_{P}Na^{+} < 130$ mEq/L;
- ü Severe hyponatremia: $_{P}Na^{+} < 125$ mEq/L.

2.4. Statistical analysis

The normality of data distribution was assessed through the Kolmogorov-Smirnov test. Data are expressed as median [interquartile range] for continuous variables and as percentages for categorical variables. Comparison between groups was performed through the Mann-Whitney U test for continuous variables and through the Chi-square test for categorical variables. Multiple continuous variables were compared through the Kruskal-Wallis test, while the Bonferroni correction was used to adjust the p-value for multiple categorical variables comparisons (*e.g.*, Chi-square test for non-2 × 2 contingency tables). Survival times among patients with different $_{P}Na^{+}$ were analyzed respectively for 7 and 30-day mortality: the log-rank test was used to identify groups with different survival probabilities and Kaplan-Meier plots were used for graphical representations. Then, variables found to be predictive of mortality with $p < 0.10$ at the univariate analysis were introduced into a Cox proportional hazard model. Considering the distinct difference between patients with moderate/severe hyponatremia and patients with mild $_{P}Na^{+}$ derangement/eunatremia, a further comparison was then performed by constituting two non-pre-specified groups: “moderate-to-severe hyponatremia” group *vs.* “eunatremia + mild hyponatremia”. Similarly, a Cox proportional hazard model was built to identify independent predictors of mortality at 7 and 30-day in the overall population, including as categorical variables “eunatremia + mild hyponatremia”, and “moderate-to-severe hyponatremia” or hypernatremia.

Statistical significance was set at two-tailed $p < 0.05$. The statistical analysis was performed with MedCalc 19.3.1 software (Mariakerke, Belgium).

3. Results

3.1. Patients

Among the 1132 patients included in the primary analysis of the Need-Speed trial [12], 890 patients with a definitive diagnosis of sepsis were considered eligible. Eleven of them were excluded because $_{P}Na^{+}$ was not available: the analysis was therefore performed on 879 patients. The flowchart of patients’ selection is reported in **Supplementary Material S1**. The main characteristics of the overall sample are presented in **Table 1**.

3.2. Prognostic value of $_{P}Na^{+}$ in the overall sepsis population

The prognostic value of $_{P}Na^{+}$ was investigated in the septic population according to 7-day (n = 85, 9.7%) and 30-day (n = 173, 19.7%) mortality. At both endpoints $_{P}Na^{+}$ was found to be higher in non-survivors compared to survivors. The main demographic, physical and laboratory characteristics of survivors and non-survivors at each endpoint, as well as the results of the univariate analyses, are reported in **Supplementary Material S2**. Half of the enrolled patients was admitted to the ED with a sodium derangement (48.7%), either in terms of hyponatremia (n = 378, 43.0%) or hypernatremia (n = 50, 5.7%). Compared to eunatremic patients, the dysnatremic ones had significantly higher mortality rates at 7 days, but the difference did not

Table 1
Patient characteristics.

Patient characteristics (n = 879)	
Age (years)	80 [72 - 87]
Sex (M/F)	475 / 404
HR (bpm)	100 [90 - 110]
RR (breaths per minute)	24 [20 - 28]
MAP (mmHg)	87 [77 - 97]
SpO_2 (%)	94 [92 - 96]
Hb (g/dL)	12.2 [10.8 - 13.4]
Ht (%)	37.7 [33.0 - 41.1]
WBCs ($x10^3/mm^3$)	12.90 [9.36 - 17.11]
PLTs ($x10^3/mm^3$)	222 [158 - 298]
$_pNa^+$ (mEq/L)	136 [133 - 139]
$_pK^+$ (mEq/L)	3.96 [3.57 - 4.40]
Creatinine (mg/dL)	1.08 [0.83 - 1.67]
Total bilirubin (mg/dL)	0.91 [0.66 - 1.43]
INR	1.19 [1.10 - 1.36]
Arterial pH	7.45 [7.40 - 7.48]
$PaCO_2$ (mmHg)	34.1 [30.0 - 39.7]
PaO_2 (mmHg)	69.5 [59.3 - 82.4]
$_pHCO_3$ (mmol/L)	23.7 [21.1 - 26.3]
PaO_2/FiO_2	286 [231 - 346]
Lactate (mmol/L)	1.5 [1.1 - 2.2]
CRP (mg/dL)	10.21 [3.42 - 18.83]
GCS	15 [15 - 15]
$_pNa^+$ Hypernatremic (mEq/L) (n = 50)	150 [148 - 155]
$_pNa^+$ Eunatremic (mEq/L) (n = 451)	138 [136 - 140]
$_pNa^+$ Hyponatremic (mEq/L) (n = 378)	132 [129 - 133]
$_pNa^+$ Mild Hyponatremic (n = 269)	133 [131 - 134]
$_pNa^+$ Moderate Hyponatremic (n = 89)	128 [127 - 129]
$_pNa^+$ Severe Hyponatremic (n = 20)	122 [120 - 124]

CRP: C-reactive protein; GCS: Glasgow Coma Scale; Hb: hemoglobin; Ht: hematocrit; HR: heart rate; INR: international normalized ratio; MAP: mean arterial pressure; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; PaO_2/FiO_2: ratio between partial pressure of oxygen and fractional inspired oxygen; PLTs: platelets; RR: respiratory rate; SpO_2: peripheral oxygen saturation; WBCs: white blood cells; $_pHCO_3$: plasma bicarbonate concentration; $_pK^+$: plasma potassium concentration; $_pNa^+$: plasma sodium concentration.

reach statistical significance at 30 days (11.9% *vs.* 7.5% p = 0.038 and 22.2% *vs.*17.3% p = 0.082, respectively) (Table 2).

When dysnatremic patients were further divided according to the nature of the sodium derangement, hypernatremia was associated with significantly higher mortality rates at both endpoints compared to eunatremia and hyponatremia (p<0.0001 for both). No significant difference was observed between eunatremic and hyponatremic patients (Table 2).

In order to detect a possible confounding role of hyperglycemia-related hyponatremia, in 123 patients with plasma glucose concentration ≥ 200 mg/dL we adjusted $_pNa^+$ values through the Hillier formula [23]. With such operation, only 48 patients (5.5%) were classified differently: three patients shifted from eunatremia to hypernatremia and the remaining ones from hyponatremia to eunatremia, with no significant changes in mortality rates among groups.

3.3. Hyponatremia in the overall sepsis population

As pre-specified, a subsequent analysis was performed by excluding hypernatremic patients and by dividing the hyponatremic ones in three groups according to the severity of $_pNa^+$ derangement: mild (n = 269, 71.2%), moderate (n = 89, 23.5%) and severe (n = 20, 5.3%) hyponatremia. The comparison performed among these three groups and patients with eunatremia highlighted a significant difference in mortality rates at 7 and 30 days. However, when the p-value was adjusted for multiple comparisons, only moderate hyponatremia *vs.* mild hyponatremia, both at 7 and 30 days, confirmed a statistical significance (respectively p = 0.008 and p = 0.008) (Table 2).

Moreover, the "moderate-to-severe hyponatremia" group showed a significantly higher mortality at each endpoint compared to the "eunatremia + mild hyponatremia" one (p = 0.004 and p = 0.007 at 7 and 30 days, respectively) (Table 2). When $_pNa^+$ values were corrected for glucose levels, only 13 hyponatremic patients (3.4%) were classified differently: two patients shifted from severe to moderate and eleven from moderate to mild hyponatremia, again with no changes in mortality among groups.

Table 2
Comparison of mortality rates at 7 and 30 days according to different degrees of sodium derangements.

	7-day mortality Non-survivors	%	30-day mortality Non-survivors	%
Dysnatremia	51	11.9%	95	22.2%
Eunatremia	34	7.5% [a]	78	17.3%
Hyponatremia	33	8.7% [b]	70	18.5% [c]
Eunatremia	34	7.5% [b]	78	17.3% [c]
Hypernatremia	18	36.0%	25	50.0%
Eunatremia	34	7.5%	78	17.3%
Mild hyponatremia	16	5.9%	40	14.9%
Moderate hyponatremia	14	15.7% [d]	25	28.1% [e]
Severe hyponatremia	3	15.0%	5	25.0%
Eunatremia + mild hyponatremia	50	6.9%	118	16.4%
Moderate-to-severe hyponatremia	17	15.6% [f]	30	27.5% [g]

The Chi-square test was used to compare mortality rates of each row (notably Dysnatremia *vs.* Eunatremia, Hyponatremia *vs.* Eunatremia *vs.* Hypernatremia, Eunatremia *vs.* Mild hyponatremia *vs.* Moderate hyponatremia *vs.* Severe hyponatremia and Eunatremia + mild hyponatremia *vs.* Moderate-to-severe hyponatremia), with the Bonferroni correction for multiple comparisons, as appropriate. Percentages refer to the overall population.

[a] statistically significant *vs.* Dysnatremia on 7-day mortality.
[b] statistically significant *vs.* Hypernatremia on 7-day mortality.
[c] statistically significant *vs.* Hypernatremia on 30-day mortality.
[d] statistically significant *vs.* Mild hyponatremia on 7-day mortality.
[e] statistically significant *vs.* Mild hyponatremia on 30-day mortality.
[f] statistically significant *vs.* Eunatremia + mild hyponatremia on 7-day mortality.
[g] statistically significant *vs.* Eunatremia + mild hyponatremia on 30-day mortality.

3.4. Survival analysis in the overall sepsis population

A survival analysis was performed by dividing patients in the above-mentioned categories. The Kaplan-Meier curves that graphically show comparisons between eunatremia *vs.* dysnatremia and between "eunatremia + mild hyponatremia" *vs.* "moderate-to-severe hyponatremia" are presented in Fig. 1 and **Supplementary Material S3**, respectively. When hypernatremia was added to the latter analysis, a significant

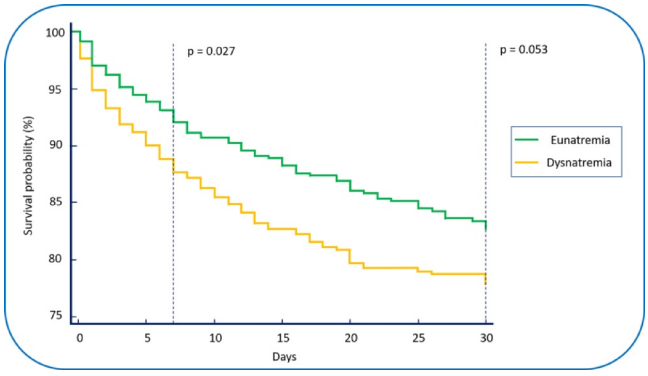

Fig. 1. Kaplan-Meier curve for the comparison of 7 and 30-day mortality between eunatremic *vs.* dysnatremic patients. As indicated by the p-values for the log-rank tests, statistical significance was reached only at 7 days.

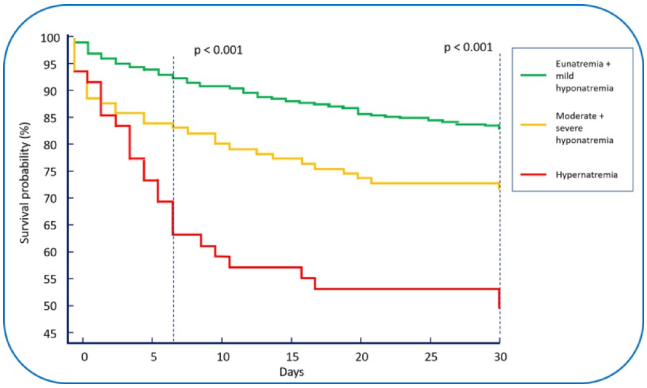

Fig. 2. Kaplan-Meier curve for the comparison of 7 and 30-day mortality between patients presenting eunatremia + mild hyponatremia *vs.* moderate-to-severe hyponatremia *vs.* hypernatremia. As indicated by the *p*-values for the log-rank tests, statistical significance was reached at both endpoints.

difference was observed in terms of survival between the three groups (Fig. 2).

A Cox proportional hazard model was built to identify independent predictors of mortality at 7 and 30-day in the overall population. Since both hyponatremia and hypernatremia were associated to higher mortality rates (**Supplementary Material S4**), $_{p}Na^{+}$ was not embedded in the model as a continuous variable. On the contrary, the model included a categorical variable *i.e.* "eunatremia + mild hyponatremia", and "moderate-to-severe hyponatremia" or hypernatremia. These categories were selected based on our previous analysis. The Cox proportional hazard identified as independent predictors of both 7 and 30-day mortality "moderate-to-severe hyponatremia" (HR 4.89 [2.38–10.03] and 1.79 [1.07–3.01], respectively) and hypernatremia (HR 3.52 [1.58–7.82] and 2.14 [1.17–3.92], respectively), together with age and plasma lactate (Table 3). Amongst the other variables significantly associated to mortality at the univariate analysis, at the multivariate one the GCS did not emerge as independent predictor of mortality either at 7 or at 30 days. Of note, sex differences were not associated either with different distribution of sodium derangements or with mortality rates at both endpoints.

3.5. Respiratory tract infection related (RTI-r) sepsis population

Five hundred forty-nine patients (62.5%), out of the whole group of 879 patients, presented clinical, radiological or microbiological findings suggestive of RTI-r sepsis. The characteristics of patients with RTI-r sepsis and with sepsis from other sites (non-RTI-r sepsis) are reported in **Supplementary Material S5**. Mortality rates were significantly higher in RTI-r sepsis compared to non-RTI-r sepsis patients both at 7 and 30 days (log-rank test: $p = 0.001$ and $p < 0.0001$, respectively) (**Supplementary Material S6**).

3.6. Sodium derangements in RTI-r sepsis and non-RTI-r sepsis population

Forty-seven percent of RTI-r sepsis patients presented a sodium derangement: 39.5% were hyponatremic and 7.1% were hypernatremic. Furthermore, among hyponatremic patients, the derangement was mild in 70.5%, moderate in 23.5% and severe in 6.0%. Compared to the non-RTI-r sepsis group, no significant difference was observed in the prevalence of sodium derangements ($p = 0.132$). When the type of sodium derangement was compared among the two populations, hypernatremia emerged to be more frequent in RTI-r sepsis and hyponatremia more frequent in non-RTI-r sepsis patients (**Supplementary Material S7**).

3.7. Prognostic value of $_{p}Na^{+}$ and survival analysis in the RTI-r sepsis population

When the characteristics of survivors and non-survivors were compared in RTI-r sepsis patients, $_{p}Na^{+}$ was found to be significantly higher in non-survivors both at 7 ($p = 0.045$) and 30 days ($p = 0.028$) (**Supplementary Material S8**). As for the overall sepsis population, mortality rates were significantly higher in dysnatremic patients both at 7 and 30 days. When dysnatremia was divided in hyponatremia and hypernatremia, mortality was significantly higher in hypernatremic patients at both endpoints (**Supplementary Material S9**). Again, we excluded hypernatremic patients and divided the remaining subjects in four groups (notably, eunatremia, mild, moderate and severe hyponatremia): only the mortality rate between moderate hyponatremia and eunatremia was significantly different ($p = 0.008$). When such patients were combined in the same previous two larger groups, mortality rates were significantly higher in those with "moderate-to-severe hyponatremia" compared to those with "eunatremia + mild hyponatremia" at both endpoints (**Supplementary Material S9**).

Then, survival analyses were performed according to the same combination of categories as for the general population (**Supplementary Material S10**). The Cox proportional hazard model subsequently built, identified both "moderate-to-severe hyponatremia" and hypernatremia as independent predictors of both 7 and 30-day mortality (**Supplementary Material S11**).

3.8. Prognostic value of pNa^{+} in the non-RTI-r sepsis population

On the contrary, no differences were found in pNa^{+} between survivors and non-survivors in the non-RTI-r sepsis population. Furthermore, when these patients were divided in the same categories listed in the previous paragraph, sodium derangements of any kind (either hyponatremia or hypernatremia) or degree (mild, moderate or severe hyponatremia, or even combined eunatremia + mild hyponatremia and moderate-to-severe hyponatremia) were not associated with

Table 3
7 and 30-day independent predictors of mortality in the overall population.

	7-day mortality				30-day mortality		
	HR	95% CI	*p*-value		HR	95% CI	*p*-value
Moderate-to-severe hyponatremia	4.89	2.38 - 10.03	<0.0001	Moderate-to-severe hyponatremia	1.79	1.07 - 3.01	0.029
Hypernatremia	3.52	1.58 - 7.82	0.002	Hypernatremia	2.14	1.17 - 3.92	0.014
Plasma lactate	1.15	1.05- 1.26	0.002	Plasma lactate	1.18	1.09- 1.28	<0.0001
Age	1.04	1.01 - 1.07	0.013	Age	1.04	1.02 - 1.06	0.001
Heart rate	1.02	1.00 - 1.03	0.046	PaO_2/FiO_2	0.99	0.99 - 0.99	0.001
Arterial pH	0.01	0.00 - 0.43	0.015	SpO_2	0.96	0.92 - 0.99	0.011
				Hb	0.88	0.79 - 0.97	0.012

The Table shows the HR resulted from the multivariate analysis conducted through Cox proportional hazard regression models.
CI: confidence interval; Hb: hemoglobin; HR: hazard ratio; PaO2/FiO2: ratio of arterial oxygen partial pressure over the oxygen inspired fraction; SpO2: peripheral oxygen saturation.

higher mortality rates both at 7 and 30 days.

4. Discussion

This subgroup analysis of the Need-Speed trial shows that in septic patients, both hypernatremia and moderate-to-severe hyponatremia at ED presentation are independent predictors of mortality at both 7 and 30 days. When considering only patients with RTI-r sepsis, similar results were observed.

Detecting which septic patients are at higher risk of death from the first hours is a real need for the emergency and critical care physician. As a matter of fact, even the existing guidelines do not provide elements for a different management according to the *a priori* patient's risk [24]. Therefore, the same treatment is suggested for patients who will likely have a less severe clinical course as well as for patients who will require a more aggressive therapeutic management. To overcome this issue and stratify the risk of death, different scores have been developed. However, they require the collection of many information and have been validated only in the ICU [25–27]. As the first medical contact of septic patients is at ED presentation, simple and rapidly available information are needed to detect patients at higher risk.

Beyond serum biomarkers measurement, data from routinely performed biochemical analyses have been proposed for this purpose, with encouraging results. Semeraro et al.[28]. have shown that D-Dimer could predict mortality in septic patients at ED admission, provided that its value is corrected for thrombin and fibrin generation. The prognostic role of lactate has been recognized [29], although not the initial measurement, but rather its variation over time has the highest prognostic value [30,31]. Again, the venous-arterial difference in the carbon dioxide partial pressure (PCO_2-gap) has been shown to predict mortality in patients with sepsis at ED admission [32], but its computation may not be practical in the ED. Thus, stratifying patients' prognosis simply on the first measurement of plasmatic sodium, without the need of further measurements or score calculation, may be very helpful in detecting patients who will need more intensive treatment.

$_pNa^+$ derangements are frequently encountered in the general hospitalized population [33,34], and it is observed in up to 5% and 35% of patients for hypernatremia and hyponatremia, respectively [35,36]. However, in critically ill patients their incidence is estimated to be higher, with direct impact on patients' outcome [37,38]. As a matter of fact, in ICU patients, both the presence and the degree of hypernatremia are indicative of the severity of the underlying disease, and are related to increased mortality [39,40] and hyponatremia is associated to an increased ICU and in-hospital length of stay. When $_pNa^+$ abnormalities are severe, the risk of death reaches up to 40% [41].

To this regard, our analysis confirms the prognostic role of both hypernatremia and moderate-to-severe hyponatremia in the specific population of septic patients, even though we cannot establish whether such sodium alterations are causative or rather associated to sepsis development. However, compared to the previous studies conducted in the ICU, we show that such predictive power can be detected very early, during the first medical contact in the ED, thus providing an immediate hint for risk stratification.

In the first part of our study, we aimed at analyzing the overall septic population of the Need-Speed cohort, regardless of the primary site of infection. Interestingly, we confirm that hypernatremia is less common than hyponatremia. However, the mortality rates of this group of septic patients were 36% and 50% at 7 and 30 days, respectively, which is slightly higher than reported in literature [39,40]. As hypernatremia is more often related to a free water deficit issue rather that sodium homeostasis, in patients admitted to the ED with sepsis, thus presenting both absolute and relative hypovolemia [42], failure of fluid resuscitation efforts becomes more likely [37,43,44]. In this subgroup, due to the relatively small number of patients, we could not perform a further analysis on mortality according to the severity of hypernatremia. However, at the multivariate analysis, hypernatremia emerged as an independent risk factor of mortality with a hazard ratio of 3.5 (**Table 3**).

On the other hand, patients with hyponatremia showed a dichotomous behavior. In fact, those with mild hyponatremia had no increased risk of dying compared to eunatremic patients. This is not surprising, as mild hyponatremia is the most common type of electrolyte disturbance in hospitalized patients and, in many cases, it is not related to a real reduction in the total amount of sodium, but it is rather the manifestation of a chronic medical condition [22,33,45]. Although it is often asymptomatic, it has been suggested that even borderline derangements of sodium concentration may worsen patients' prognosis [46]. On the opposite, in our cohort the two more severe degrees of hyponatremia were similarly associated to an increased mortality. To highlight this difference, we combined moderate and severe hyponatremia and demonstrated that such derangements are independently responsible for a 5-fold increase in mortality at 7 days in septic patients, and that such prediction can be observed in the ED at the first medical contact (**Table 3**).

When patients were divided according to the source of infection, we observed different results in the RTI-r sepsis group and in the non-RTI-r sepsis group: in fact, sodium derangements were strongly associated with mortality in patients with sepsis of respiratory tract origin, while no association was found in sepsis from other sources. This was not surprising, since RTIs are often accompanied by sodium derangements, especially hyponatremia, which independently predicts a worse outcome [19] and is therefore included in many prognostic scores, one for all the Pneumonia Severity Index or PSI [47]. In this regard, our results confirm data from the literature, as the 7-day risk of mortality was increased by 5 times in moderate-to-severe hyponatremic patients. Moreover, we demonstrated that also hypernatremia is independently responsible for a similar decrease in survival at 7 days. Again, such information can be derived at ED admission: since mortality of RTI-r sepsis is higher compared to the one from other sources [48], such an early stratification may prompt aggressive therapeutic management, eventually leading to a more favorable outcome.

4.1. Limitations

First, this is a sub-group analysis of prospectively enrolled patients for another trial [12]. Thus, our outcomes were not pre-specified at the time of the study design. Similarly, patients' inclusion was already performed. Nevertheless, as only 1% of such septic patients had to be excluded from our study, we judged the selection bias in our subgroup analysis as "low". Second, we used the Sepsis-2 criteria for patient's inclusion, which were published long time ago. However, the Need-Speed Trial was conducted between 2013 and 2015, while the latest Sepsis-3 criteria have appeared only in 2016 [49]. Third, we could not retrieve information related to patients' chronic treatment, or the presence of comorbidities which could have acted as possible confounders. Hence, we could not evaluate whether sodium derangements were influenced by drugs interfering with its plasmatic levels or chronic medical conditions. However, it is unlikely that such information would have affected the results of our study, as the early prognostic role of sodium derangement seems quite strong. Fourth, we recorded baseline value of plasmatic sodium, and we could not evaluate the kinetics of sodium correction during hospitalization. However, the aim of the present analysis was to identify an easy and immediate factor able to could stratify the mortality risk of patients with sepsis, at the first medical contact in the ED.

5. Conclusions

In septic patients the presence of either hypernatremia or moderate-to-severe hyponatremia at ED presentation are independent predictors of 7 and 30-day mortality. This information provides an immediate risk stratification and should promote more aggressive therapeutic

management of such patients.

Authors' contribution

LMC, FG and GCA conceived and designed the study.

MBa, LS, FP, MBe, FM, NF, GR, SD, EL, LMM and GB collected the data.

LMC, FG and MBa analyzed and interpreted the data.

LMC, FG, MBa drafted the report and all authors contributed to review it.

All authors approved the final version.

Declaration of Competing Interest

All the authors state they do not have any conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.10.003.

References

[1] Prasad PA, Fang MC, Abe-Jones Y, Calfee CS, Matthay MA, Kangelaris KN. Time to recognition of sepsis in the emergency department using electronic health record data: a comparative analysis of systemic inflammatory response syndrome, sequential organ failure assessment, and quick sequential organ failure assessment. Crit Care Med 2020;48:200–9. https://doi.org/10.1097/CCM.0000000000004132.

[2] Lee JT, Mikkelsen ME. Risk stratification tools in sepsis: from acute physiology and chronic health evaluation to quick sequential organ failure assessment*. Crit Care Med 2019;47:1159–61. https://doi.org/10.1097/CCM.0000000000003859.

[3] Hariri G, Joffre J, Leblanc G, Bonsey M, Lavillegrand J-R, Urbina T, et al. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. Ann Intensive Care 2019;9:37. https://doi.org/10.1186/s13613-019-0511-1.

[4] Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status *vs* serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA 2019;321:654–64. https://doi.org/10.1001/jama.2019.0071.

[5] Gavelli F, Teboul J-L, Monnet X. How can CO_2-derived indices guide resuscitation in critically ill patients? J Thorac Dis 2019;11:S1528–37. https://doi.org/10.21037/jtd.2019.07.10.

[6] Wardi G, Brice J, Correia M, Liu D, Self M, Tainter C. Demystifying lactate in the emergency department. Ann Emerg Med 2020;75:287–98. https://doi.org/10.1016/j.annemergmed.2019.06.027.

[7] Pregernig A, Müller M, Held U, Beck-Schimmer B. Prediction of mortality in adult patients with sepsis using six biomarkers: a systematic review and meta-analysis. Ann Intensive Care 2019;9:125. https://doi.org/10.1186/s13613-019-0600-1.

[8] Castello LM, Baldrighi M, Molinari L, Salmi L, Cantaluppi V, Vaschetto R, et al. The role of osteopontin as a diagnostic and prognostic biomarker in sepsis and septic shock. Cells 2019;8. https://doi.org/10.3390/cells8020174.

[9] Lemasle L, Blet A, Geven C, Cherifa M, Deniau B, Hollinger A, et al. Bioactive adrenomedullin, organ support therapies, and survival in the critically Ill: results from the French and European outcome registry in ICU study. Crit Care Med 2020;48:49–55. https://doi.org/10.1097/CCM.0000000000004044.

[10] Baldirà J, Ruiz-Rodríguez JC, Wilson DC, Ruiz-Sanmartin A, Cortes A, Chiscano L, et al. Biomarkers and clinical scores to aid the identification of disease severity and intensive care requirement following activation of an in-hospital sepsis code. Ann Intensive Care 2020;10:7. https://doi.org/10.1186/s13613-020-0625-5.

[11] Henning DJ, Bhatraju PK, Johnson NJ, Kosamo S, Shapiro NI, Zelnick LR, et al. Physician judgment and circulating biomarkers predict 28-day mortality in emergency department patients. Crit Care Med 2019;47:1513–21. https://doi.org/10.1097/CCM.0000000000003899.

[12] Mearelli F, Fiotti N, Giansante C, Casarsa C, Orso D, De Helmersen M, et al. Derivation and validation of a biomarker-based clinical algorithm to rule out sepsis from noninfectious systemic inflammatory response syndrome at emergency department admission: a multicenter prospective study. Crit Care Med 2018;46:1421–9. https://doi.org/10.1097/CCM.0000000000003206.

[13] Tupchong K, Chien C. Is procalcitonin useful in the diagnosis and treatment of acute respiratory infections in the emergency department? Ann Emerg Med 2018;72:57–8. https://doi.org/10.1016/j.annemergmed.2018.01.040.

[14] Engelhardt LJ, Balzer F, Müller MC, Grunow JJ, Spies CD, Christopher KB, et al. Association between potassium concentrations, variability and supplementation, and in-hospital mortality in ICU patients: a retrospective analysis. Ann Intensive Care 2019;9:100. https://doi.org/10.1186/s13613-019-0573-0.

[15] Dépret F, Peacock WF, Liu KD, Rafique Z, Rossignol P, Legrand M. Management of hyperkalemia in the acutely ill patient. Ann Intensive Care 2019;9:32. https://doi.org/10.1186/s13613-019-0509-8.

[16] McCarthy K, Conway R, Byrne D, Cournane S, O'Riordan D, Silke B. Hyponatraemia during an emergency medical admission as a marker of illness severity & case complexity. Eur J Intern Med 2019;59:60–4. https://doi.org/10.1016/j.ejim.2018.08.002.

[17] Harrois A, Anstey JR, Taccone FS, Udy AA, Citerio G, Duranteau J, et al. Serum sodium and intracranial pressure changes after desmopressin therapy in severe traumatic brain injury patients: a multi-centre cohort study. Ann Intensive Care 2019;9:99. https://doi.org/10.1186/s13613-019-0574-z.

[18] Cárdenas A, Solà E, Rodríguez E, Barreto R, Graupera I, Pavesi M, et al. Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study. Crit Care 2014;18:700. https://doi.org/10.1186/s13054-014-0700-0.

[19] Müller M, Schefold JC, Guignard V, Exadaktylos AK, Pfortmueller CA. Hyponatraemia is independently associated with in-hospital mortality in patients with pneumonia. Eur J Intern Med 2018;54:46–52. https://doi.org/10.1016/j.ejim.2018.04.008.

[20] Lindner G, Funk G-C, Schwarz C, Kneidinger N, Kaider A, Schneeweiss B, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. Am J Kidney Dis 2007;50:952–7. https://doi.org/10.1053/j.ajkd.2007.08.016.

[21] Levy M.M., Fink M.P., Marshall J.C., Abraham E., Angus D., Cook D., et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6. 10.1097/01.CCM.0000050454.01978.3B.

[22] Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581–9. https://doi.org/10.1056/NEJM200005253422107.

[23] Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 1999;106:399–403. https://doi.org/10.1016/s0002-9343(99)00055-8.

[24] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77. https://doi.org/10.1007/s00134-017-4683-6.

[25] Gall J-RL, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American Multicenter Study. JAMA 1993;270:2957–63. https://doi.org/10.1001/jama.1993.03510240069035.

[26] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10. https://doi.org/10.1007/bf01709751.

[27] Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically III hospitalized adults. Chest 1991;100:1619–36. https://doi.org/10.1378/chest.100.6.1619.

[28] Semeraro F, Ammollo CT, Caironi P, Masson S, Latini R, Panigada M, et al. D-dimer corrected for thrombin and plasmin generation is a strong predictor of mortality in patients with sepsis. Blood Transfus 2019:1–8. https://doi.org/10.2450/2019.0175-19.

[29] Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care 2013;3:12. https://doi.org/10.1186/2110-5820-3-12.

[30] Mitra B, Roman C, Charters KE, O'Reilly G, Gantner D, Cameron PA. Lactate, bicarbonate and anion gap for evaluation of patients presenting with sepsis to the emergency department: a prospective cohort study. Emerg Med Australas 2020;32:20–4. https://doi.org/10.1111/1742-6723.13324.

[31] Gattinoni L, Vasques F, Camporota L, Meessen J, Romitti F, Pasticci I, et al. Understanding lactatemia in human sepsis. Potential impact for early management. Am J Respir Crit Care Med 2019;200:582–9. https://doi.org/10.1164/rccm.201812-2342OC.

[32] Shetty A, Sparenberg S, Adams K, Selvedran S, Tang B, Hanna K, et al. Arterial to end-tidal carbon dioxide tension difference (CO_2 gap) as a prognostic marker for adverse outcomes in emergency department patients presenting with suspected sepsis. Emerg Med Australas 2018;30:794–801. https://doi.org/10.1111/1742-6723.13095.

[33] Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. BMJ 2006;332:702–5. https://doi.org/10.1136/bmj.332.7543.702.

[34] Castello LM, Baldrighi M, Panizza A, Bartoli E, Avanzi GC. Efficacy and safety of two different tolvaptan doses in the treatment of hyponatremia in the emergency department. Intern Emerg Med 2017;12:993–1001. https://doi.org/10.1007/s11739-016-1508-5.

[35] Molaschi M, Ponzetto M, Massaia M, Villa L, Scarafiotti C, Ferrario E. Hypernatremic dehydration in the elderly on admission to hospital. J Nutr Health Aging 1997;1:156–60.

[36] Kumar S, Berl T. Sodium. Lancet 1998;352:220–8. https://doi.org/10.1016/S0140-6736(97)12169-9.

[37] Overgaard-Steensen C, Ring T. Clinical review: practical approach to hyponatraemia and hypernatraemia in critically ill patients. Crit Care 2013;17:206. https://doi.org/10.1186/cc11805.

[38] Rosner MH, Ronco C. Dysnatremias in the intensive care unit. Contrib Nephrol 2010;165:292–8. https://doi.org/10.1159/000313769.

[39] Tsipotis E, Price LL, Jaber BL, Madias NE. Hospital-associated hypernatremia spectrum and clinical outcomes in an unselected cohort. Am J Med 2018;131:72–82. https://doi.org/10.1016/j.amjmed.2017.08.011.

[40] Polderman KH, Schreuder WO, Strack van Schijndel RJ, Thijs LG. Hypernatremia in the intensive care unit: an indicator of quality of care? Crit Care Med 1999;27:1105–8. https://doi.org/10.1097/00003246-199906000-00029.

[41] Pasantes-Morales H, Cruz-Rangel S. Brain volume regulation: osmolytes and

aquaporin perspectives. Neuroscience 2010;168:871–84. https://doi.org/10.1016/j.neuroscience.2009.11.074.
[42] Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. Ann Intensive Care 2019;9:20. https://doi.org/10.1186/s13613-019-0498-7.
[43] Beurton A, Teboul J-L, Gavelli F, Gonzalez FA, Girotto V, Galarza L, et al. The effects of passive leg raising may be detected by the plethysmographic oxygen saturation signal in critically ill patients. Crit Care 2019;23:19. https://doi.org/10.1186/s13054-019-2306-z.
[44] Ni H-B, Hu X-X, Huang X-F, Liu K-Q, Yu C-B, Wang X-M, et al. Risk factors and outcomes in patients with hypernatremia and sepsis. Am J Med Sci 2016;351:601–5. https://doi.org/10.1016/j.amjms.2016.01.027.
[45] Baldrighi M, Sainaghi PP, Bellan M, Bartoli E, Castello LM. Hyperglycemic hyperosmolar state: a pragmatic approach to properly manage sodium derangements. Curr Diabetes Rev 2018;14:534–41. https://doi.org/10.2174/1573399814666180320091451.
[46] Darmon M, Diconne E, Souweine B, Ruckly S, Adrie C, Azoulay E, et al. Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. Crit Care 2013;17:R12. https://doi.org/10.1186/cc11937.
[47] Valencia M, Badia JR, Cavalcanti M, Ferrer M, Agustí C, Angrill J, et al. Pneumonia severity index class v patients with community-acquired pneumonia: characteristics, outcomes, and value of severity scores. Chest 2007;132:515–22. https://doi.org/10.1378/chest.07-0306.
[48] Tillmann B, Wunsch H. Epidemiology and outcomes. Crit Care Clin 2018;34:15–27. https://doi.org/10.1016/j.ccc.2017.08.001.
[49] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10. https://doi.org/10.1001/jama.2016.0287.