

Prevalence and Prognostic Impact of Hyponatremia in Sepsis and Septic Shock Patients in The Intensive Care Unit: A Single Centre Experience

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ABSTRACT

Introduction: Hyponatremia is a commonly associated electrolyte disturbance in sepsis and septic shock patients in the ICU. The objective of this study was to identify the prognostic value of hyponatremia in sepsis and septic shock

Material and Methods: A prospective study conducted on sepsis and septic shock patients diagnosed prior to admission in the ICU in King Hamad University Hospital, Bahrain from January 1st 2017 to February 28th 2019. Data including age, sex, comorbidities, source of sepsis, sodium levels on days one, three, and seven. Data was correlated with the outcome (survival/death and the length of ICU stay). **Results:** Patients included were 168, 110 survived, and 58 died. Hyponatremia at day seven was associated with significantly higher mortality ($P= 0.03$). Hyponatremia at Day1 was associated with a significantly prolonged stay in the ICU ($p= 0.039$). Multivariate analysis to identify the independent predictors of mortality revealed that immunosuppression and hyponatremia at Day7 proved to be independent predictors of mortality ($P= 0.026$ and 0.039 respectively). **Conclusion:** Hyponatremia can be an independent predictor of poor outcome in septic and septic shock patients in the ICU.

Keywords: sepsis, hyponatremia, biomarkers

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INTRODUCTION

Sepsis and septic shock are among the most prevalent causes of intensive care unit (ICU) admissions. They account for around 10-50% of the mortality rate, which remains high despite extensive research, the Surviving Sepsis Campaign, and national core measures [1-5].

Sepsis is defined as “Organ dysfunction that threatens the patient’s life caused by the impaired host response to infection” [6]. However, septic shock is defined as hypotension and serum lactate level greater than two mmol/L, as well as not responding to adequate fluid resuscitation requiring the use of vasopressors to maintain the mean blood pressure of 65 mm Hg

or higher [7]. Sepsis and septic shock are considered medical emergencies that require early identification and immediate management [8–16].

Acute hyponatremia is considered one of the features of homeostasis disturbances, which is common in septic patients with an incidence reaching up to 47% [17]

Finding biomarkers which predict the outcome of sepsis is challenging [18,19]. Since electrolyte imbalance, specifically hyponatremia, is one of the commonest problems associated with sepsis and septic shock patients [20, 21]. It is, therefore, of current interest to study the evolution of sepsis in patients who have been shown to have hyponatremia.

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The aim of the present study is to identify the prevalence and prognostic impact of hypernatremia on sepsis and septic shock patients

■ MATERIALS AND METHODS

A prospective observational study, conducted on sepsis and septic shock patients that were admitted in the Intensive Care Unit (ICU) of King Hamad University Hospital, Kingdom of Bahrain over 25 months, starting from January 1st, 2017 till February 28th, 2019.

The diagnosis of sepsis and septic shock was made prior to the ICU admission.

Sepsis and septic shock were defined according to the Sepsis 3 definition using the Quick Sofa score of 2 or more [6, 7], and hypernatremia was defined as $[Na^+] > 145$ mmol/L.

The excluded patients were those aged < 18 years, those planned for “end of life care”, and patients with a previous diagnosis of hyperaldosteronism, Cushing syndrome, or diabetes insipidus.

Data collection methods, instruments used, and measurements

Data collected included demographic data (age, sex), comorbidities, source of sepsis, sodium levels on days one, three, and seven.

The source of sepsis was confirmed via a routine sepsis workup that included radiological evidence, culture and sensitivity of blood, sputum, and urine, abdominal fluid drain culture, tissue culture, and cerebrospinal fluid (CSF) analysis and cultures for suspected cases.

Various variables including demographic data, comorbidities, source of sepsis, and sodium levels on days 1, 3, and 7 were assessed against the outcome parameters, that were the length of ICU stay and mortality.

To test the predictability of sodium levels, patients were divided into patients with hypernatraemia (Na level > 145 mmol/l), eunatraemia (Na level = 135-145 mmol/l) or hyponatraemia (Na level < 135 mmol/l) on days 1,3, and 7 post-admission to the ICU

Data management and analysis plan

The data was analyzed using SPSS version 22 and Microsoft Excel 2016.

The level of significance was set at 0.05

■ RESULTS

Of 224 patients admitted to the ICU with sepsis and septic shock, 168 patients fulfilled the inclusion criteria. Demographic data, comorbidities, and sources of sepsis were analysed (Table 1).

One hundred and ten patients survived, and fifty-eight died. Regarding comorbidities, chronic kidney disease (CKD), ischemic heart disease (IHD), and immunosuppressed patients had significantly higher mortality. ($P = 0.046, 0.046, \text{ and } 0.002$) respectively. (Table 1)

CKD and diabetes mellitus (DM) were associated with a significantly longer length of stay. ($P = 0.003, 0.011$) respectively (Table 2).

Sodium levels were recorded and assessed against the outcome parameters. Hypernatremia at Day1 and Day3 did not show any positive correlation with outcome. However, hypernatraemia at day seven was associated with significantly higher mortality ($P = 0.388, 0.709, \text{ and } 0.030$, respectively). (Table 3) However, hypernatraemia at Day1 was associated with a significantly prolonged stay in the ICU ($p = 0.039$). (Table 4)

Multivariate analysis to identify the independent predictors of mortality (Table 2) revealed that immunosuppression and hypernatraemia at Day7 proved to be independent predictors of mortality ($P = 0.026$ and 0.039 respectively) (Table 5).

■ DISCUSSION

The results of the study showed that hypernatremia on the Day7 was associated with high mortality in septic patients. Moreover, hypernatremia on the Day1 was associated with prolonged length of ICU stay of septic patients.

The definition of hypernatremia used in this study was a serum sodium concentration > 145 mmol/L [22,23]. This serum sodium level was considered as the upper limit of normal and was used to test the correlation between even the mildest degrees of hypernatremia in septic patients and the outcome represented by both ICU mortality and length of stay in the ICU.

Previous studies have reported higher morbidity and mortality in the general ICU population with hypernatremia. They defined hypernatremia as serum sodium > 149 mmol/l [23-30].

In the current study, the decision was taken to test the effect of both initial and developed hypernatremia

Table 1. Relationships between Outcome and Demographic data, Comorbidities, and Sources of Sepsis (n= 168)

	Total (n= 168)	Outcome		p
		Survival (n= 110)	Death (n= 58)	
Gender				
Male	92 (54.8%)	60 (54.5%)	32 (55.2%)	0.938
Female	76 (45.2%)	50 (45.5%)	26 (44.8%)	
Age (years)				
Median (Min. – Max.)	69 (26 – 104)	67 (26 – 97)	74 (34 – 104)	0.001*
Mean ± SD.	68.5 ± 13.3	72.7 ± 10.9	66.3 ± 14	
Comorbidities				
Diabetes mellitus	116 (69%)	71 (64.5%)	45 (77.6%)	0.082
Chronic kidney disease	53 (31.5%)	29 (26.4%)	24 (41.4%)	0.046*
High blood pressure	131 (78%)	81 (73.6%)	50 (86.2%)	0.062
Ischemic heart disease	63 (37.5%)	33 (30%)	30 (51.7%)	0.046*
Immunosuppressed	44 (73.8%)	20 (20)	24 (41.4%)	0.002*
Source of sepsis				
Unknown	7 (4.2%)	3 (5.2%)	4 (3.6%)	0.694
Abdomen	19 (11.3%)	12 (10.9%)	7 (12.1%)	0.821
Lungs	84 (50%)	52 (47.3%)	32 (55.2%)	0.330
Urinary Tract	45 (26.8%)	29 (26.4%)	16 (27.6%)	0.865
Central nervous system	2 (1.2%)	1 (0.9%)	1 (1.7%)	1.000
Soft Tissue/Ulcer	24 (14.3%)	16 (14.5%)	8 (13.8%)	0.895
Orthopedic	1 (0.6%)	1 (0.9%)	0 (0%)	1.000
Blood stream infection	3 (1.8%)	2 (3.4%)	1 (0.9%)	0.274

t: Student t-test; U: Mann Whitney test; p: p-value for the association between Outcome and different parameters; *: Statistically significant at $p \leq 0.05$

Table 2. Relationships between the length of ICU stay and Demographic data, Comorbidities, and Source of Sepsis (n=168)

	length of ICU stays		p
	Median (Min. – Max.)	Mean ± SD.	
Gender			
Male	10 (1 – 120)	17 ± 20.5	0.892
Female	9.5 (1 – 210)	21.8 ± 32.3	
Comorbidities			
Diabetes mellitus	12 (1 – 210)	21.8 ± 29.5	0.011*
Chronic kidney disease	14 (1 – 124)	25.2 ± 26.1	0.003*
High blood pressure	10 (1 – 210)	20.8 ± 28.9	0.229
Ischemic heart disease	10 (1 – 210)	20.1 ± 30.5	0.999
Immunosuppressed	10.5 (2 – 120)	21.5 ± 25.7	0.406
Source of sepsis			
Unknown	21 (5 – 120)	42.7 ± 44.2	0.046*
Abdomen	19 (3 – 57)	22.9 ± 19.3	0.101
Lungs	11.5 (1 – 210)	24 ± 34.1	0.292
Urinary Tract	9 (1 – 120)	16 ± 22.5	0.277
Central nervous system	20 (15 – 25)	20 ± 7.1	0.371
Soft Tissue/Ulcer	12.5 (2 – 68)	16.6 ± 15.8	0.652
Orthopedic		5#	-
Bloodstream infection	8 (2 – 21)	10.3 ± 9.7	0.606

p: p-value for the association between length of ICU stay and different parameters; *: Statistically significant at $p \leq 0.05$; #: Excluded from the association due to a small number of case (n = 1)

Table 3. Relation between Outcome and Sodium levels on Days 1, Days 3, and Days 7 (n= 168)

	Total (n= 168)	Outcome		p
		Survival (n= 110)	Death (n= 58)	
Serum Na (day1)				
Low (<135)	67 (39.9%)	42 (38.2%)	25 (43.1%)	0.388
Normal (135 – 145)	91 (54.2%)	64 (58.2%)	27 (46.6%)	
High (>145)	10 (6%)	4 (3.6%)	6 (10.3%)	
Median (Min. – Max.)	136 (109–152)	136 (114–151)	135 (109–152)	
Mean ± SD.	135.6± 6.6	135.6± 5.9	134.8± 7.9	
Serum Na (day3)				
Low (<135)	39(26.4%)	25 (25%)	14 (29.2%)	0.709
Normal (135 – 145)	95(64.2%)	69 (69%)	26 (54.2%)	
High (>145)	14(9.5%)	6 (6%)	8 (16.7%)	
Median (Min. – Max.)	138 (113–155)	138 (118–155)	137 (113–152)	
Mean ± SD.	137.9 ± 5.8	137.8 ± 5	137.8 ± 7.3	
Serum Na (day7)				
Low (<135)	22 (19.5%)	16 (22.2%)	6 (14.6%)	0.030*
Normal (135 – 145)	70 (61.9%)	47 (65.3%)	23 (56.1%)	
High (>145)	21 (18.6%)	9 (12.5%)	12 (29.3%)	
Median (Min. – Max.)	139 (120–154)	138 (120–154)	141 (130–152)	
Mean ± SD.	139.3 ± 6.2	138.3 ± 6	141.2 ± 6.3	

t: Student t-test; U: Mann Whitney test; p: p-value for the association between Outcome and different parameters; *: Statistically significant at $p \leq 0.05$

Table (4): Relation between the Length of ICU stay and Sodium levels on Days 1, Days 3, and Days 7 (n=168)

	length of ICU stays		p
	Median (Min. – Max.)	Mean ± SD.	
Serum Na (day1)			
Low (<135)	12 (1 – 210)	20 ± 32.5	0.039*
Normal (135 – 145)	8 (1 – 112)	16.8 ± 20.6	
High (>145)	29.5 (5 – 88)	34.4 ± 27.8	
Serum Na (day3)			
Low (<135)	12 (3 – 120)	17.8 ± 20.6	0.815
Normal (135 – 145)	12 (1 – 210)	23.2 ± 30.6	
High (>145)	11.5 (3 – 80)	20.6 ± 20.5	
Serum Na (day7)			
Low (<135)	16 (8 – 88)	21.4 ± 18.8	0.373
Normal (135 – 145)	17.5 (1 – 210)	27.1 ± 33.2	
High (>145)	21 (3 – 80)	32 ± 24.6	

p: p-value for the association between length of ICU stay and different parameters; *: Statistically significant at $p \leq 0.05$; #: Excluded from the association due to a small number of case (n = 1)

in ICU septic patients. To do this, sodium levels on the Day1, Day3, and Day7 were collected and examined. The correlation between the duration of hypernatremia in septic ICU patients and the outcome was not calculated. Both O'Donoghue et al. (2009) and Michael D. Waite et al. (2013) failed to find an association between the duration of hypernatremia and mortality [24, 31].

A study by Van De Louw et al. (2014) showed that 31% of them developed hypernatremia by the fifth-day post-ICU admission [37]. However, another study showed that 47.1% of the patients developed hypernatremia during their stay in an ICU [38] compared to 18.7% by the Day 7 in the present study. The mechanism of the development of hypernatremia can be due

Table 5. Univariate and multivariate analysis for independent predictors of mortality

	Univariate		#Multivariate	
	p	OR (95%C.I)	p	OR (95%C.I)
Age (years)	0.004*	1.040(1.013 – 1.068)	0.114	1.034(0.992 – 1.078)
Gender	0.938	1.026(0.541 – 1.944)		
Source of sepsis				
Unknown	0.637	1.445(0.312 – 6.689)		
Abdomen	0.822	1.121(0.416 – 3.022)		
Lungs	0.331	1.373(0.725 – 2.600)		
Urinary Tract	0.865	1.064(0.520 – 2.175)		
Central nervous system	0.649	1.912(0.117 – 31.142)		
Soft Tissue/Ulcer	0.895	0.940(0.376 – 2.348)		
Orthopaedic	1.000	-		
Bloodstream infection	0.271	3.893(0.345 – 43.866)		
Comorbidities				
Diabetes mellitus	0.085	1.901(0.916 – 3.947)		
Chronic kidney disease	0.048*	1.972(1.006 – 3.865)	0.562	1.32(0.521 – 3.326)
High blood pressure	0.066	2.238(0.948 – 5.280)		
Ischemic heart disease	0.006*	2.500(1.296 – 4.822)	0.204	1.77(0.732 – 4.303)
Immunosuppressed	0.001*	3.176(1.558 – 6.478)	0.026*	2.99(1.141 – 7.848)
Serum Na (day1)	0.489	0.983(0.937 – 1.031)		
Serum Na (day3)	0.630	1.015(0.956 – 1.077)		
Serum Na (day7)	0.020*	1.082(1.013 – 1.157)	0.039*	1.08(1.004 – 1.154)

to dehydration associated with fever, hyperglycaemia, diarrhoea, nasogastric drainage, in addition to the loss of the patients' ability to maintain their water intake while being sedated and mechanically ventilated [31].

Besides, other mechanisms of hypernatremia can be the volume of 0.9% saline infused during the first 48 hours of admission [31], renal impairment together with renal water loss [17,32], and the administration of loop diuretics [34,35].

In our studied group, none of the patients received any diuretics. However, 31.5% were known to have chronic kidney disease (CKD). Additionally, all patients received the same initial resuscitation as recommended by the surviving sepsis campaign guidelines using crystalloids, 0.9% saline or lactated Ringer's solution [4]. The volume of any further fluid was directed by various techniques, which included the passive leg raising test, pulse contour cardiac output (PiCCO), and echocardiography. Moreover, continuous renal replacement therapy (CRRT) was commenced early in all patients who had or developed acute kidney injury (AKI) in the ICU. Previous studies have shown that the use of renal replacement therapy, either continuous or intermittent, will reduce the incidence of hypernatremia [43,44].

Accordingly, the previously mentioned management strategies adopted in our study group may explain the lower incidence of hypernatremia (18.7%).

In accord with previous observational studies on hypernatremia and sepsis, this prospective study shows significantly higher mortality rates and prolonged ICU stay in patients with hypernatremia [37, 38].

Although our study was conducted prospectively on a large number of patients, there were several limitations. Firstly, the correlation between the degree and duration of hypernatremia with the outcome was not tested. Secondly, only the effect of hypernatremia on Day 1, Day 3 and Day 7, was studied. The correlation of hypernatremia with sodium levels measured daily for at least the first ten days of admission may have given more precise results.

■ CONCLUSION

Hypernatremia can be an independent predictor of poor outcome in septic and septic shock patients in the ICU.

■ CONFLICT OF INTEREST

None to declare.

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