

Retrospective analysis of patients diagnosed with severe hyponatraemia in the emergency department

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ABSTRACT

Background. We investigated the demographic, aetiological and clinical characteristics of patients who presented to the emergency department and had severe hyponatraemia.

Methods. We retrospectively evaluated 1171 patients who presented to the emergency department and were diagnosed with severe hyponatraemia.

Results. Over half the patients studied were women (53.5%). The mean age of women was higher ($p < 0.0001$). The most common complaint was dyspnoea (16.8%) and 42.5% of the patients had an oral intake disorder. In addition, 22.3% of the patients were on loop diuretics. About 76.3% of patients were conscious, and the mean sodium level of these patients was higher than the mean sodium level of those who responded to verbal and painful stimuli ($p < 0.001$). Severe isolated hyponatraemia was observed in 61.8% of the patients. The mortality rate was 12.8%. There was no difference between the mean sodium levels of the deceased and discharged patients ($p = 1.0$). The mortality rate was higher in patients who had a history of cirrhosis and cancer, but was lower in patients with a history of coronary artery disease ($p = 0.0002$, $p < 0.0001$ and $p = 0.04$, respectively).

Conclusion. Severe hyponatraemia was more prevalent in women, serum sodium levels were higher in conscious patients, and the mortality rate was higher in patients who had a history of cirrhosis and cancer. We found that the mean serum sodium levels did not help in distinguishing between the deceased and discharged patients.

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INTRODUCTION

Electrolyte imbalance is a commonly encountered concern in the emergency department. The most common type of electrolyte imbalance in patients presenting to the emergency department is hyponatraemia (44%).^{1,2} Serum sodium levels lower than 135 mEq/L and 125 mEq/L indicate hyponatraemia and severe hyponatremia, respectively.^{3,4} The proportion of patients who present to the emergency department and have severe hyponatraemia has been reported to be 0.9%–3%.^{3–5} Severe hyponatraemia is associated with high morbidity and mortality and manifests with a variety of clinical symptoms.⁴

The aetiology of hyponatraemia varies depending on the type of hyponatraemia. Heart failure, cirrhosis, nephrotic syndrome, inappropriate antidiuretic hormone, primary adrenal insufficiency, hypothyroidism, infections, third-space losses (burns, pancreatitis, ileus and peritonitis), diarrhoea, vomiting, medication use (diuretics, etc.), strenuous activities and high temperature may cause hyponatraemia.^{2–4}

Hyponatraemia can manifest with variable clinical signs depending on the underlying cause and type of onset. Symptoms depend on the degree and progression rate of hyponatraemia.⁴ Acute (<48 hours) and severe symptomatic hyponatraemia is a medical emergency.³ It may lead to a wider spectrum of clinical symptoms ranging from obscure to severe and even life-threatening conditions and it is associated with increased mortality, morbidity, and a longer length of hospital stay in patients presenting with various comorbid conditions. However, the management of such patients remains challenging.⁴ Therefore, a systematic approach including medical history, thorough physical examination and laboratory data is essential for diagnosis and treatment.³ Although severe hyponatraemia is associated with high mortality and morbidity, only a limited number of studies have investigated the risk factors for this disorder in patients presenting to the emergency department.²

We aimed to investigate the demographic, aetiological and clinical features of patients with severe hyponatraemia presenting to the emergency department and to determine possible risk factors.

METHODS

We included patients aged 18 years and older who presented to the emergency department of Mersin University Medical Faculty Hospital between 1 January 2012 and 31 December 2016. We retrospectively screened patients who had serum sodium levels <125 mEq/L in the laboratory tests from the hospital information management system. We excluded pregnant women,

patients with missing data, and those with pseudohyponatraemia from the analysis.

We noted important data such as the age and gender of the patients, season at admission, chronic diseases, regular drug use that could cause hyponatraemia (loop diuretics, thiazide diuretics, potassium-sparing diuretics, chemotherapeutic drugs, non-steroidal anti-inflammatory drugs [NSAIDs], carbamazepine, fluoxetine, haloperidol and amitriptyline), history of transurethral prostate resection (TURP) or another procedure within the previous few weeks, presence of oral intake disorders,⁶ presenting complaints, level of consciousness, serum osmolarity, emergency department and hospital end-points (admission, discharge, referral, discharge against medical advice, death) and length of hospital stay on a previously prepared data form.

We evaluated the patients' level of consciousness according to the AVPU scale (A: Alert; V: Verbal [responding to verbal stimuli]; P: Pain [responding to painful stimuli]; and U: Unresponsive [no response to stimuli]).⁷ The Clinical Research Ethics Committee of the Rectorate of Mersin University (dated 9 November 2017; no. 2017/315) approved this study protocol.

Statistical analysis

We expressed continuous variables as mean and standard deviation. We used Student's *t*-test to analyse the difference between the two mean values. We also used analysis of variance to determine if there was a difference between the mean values of more than two groups. To determine the group that caused the differences, we used the *post-hoc* Tukey test. We expressed categorical variables with numbers and percentages. We employed the *z*-test to determine if there was a difference between the proportions of the two groups. A value of $p < 0.05$ was considered statistically significant. We used MedCalc®17.9.7 software package for data analysis.

RESULTS

We found that 405 192 patients presented to the adult emergency department of Mersin University Medical Faculty between 1 January 2012 and 31 December 2016. Of these patients, 1365 were found to have severe hyponatraemia in the tests conducted at the emergency department. In total, 123 of these patients were excluded due to missing data, 10 due to pregnancy, and 61 due to the lack of severe hyponatraemia in the follow-up blood tests. Thus, we included 1171 patients including 625 women (53.5%) and 546 men (46.5%). In total, 26.7%, 25.1%, 25% and 23.1% of the patients had presented to the hospital in the winter, summer, spring and autumn, respectively. The mean (SD) age of the patients was 66.8 (15.12) years. We found that the rate of women presenting was higher ($p=0.001$), and the mean (SD) age of women was 69.1 (15.7) years, whereas the mean (SD) age of men was 64.3 (14.0) years ($p < 0.0001$). We also found that the most common presenting complaint was dyspnoea; 42.3% of the patients had a history of hypertension and 84.8% of the patients had hypo-osmolar serum. Table I shows the distribution of patients according to presenting complaints, chronic diseases and serum osmolarity.

Considering the factors that could cause hyponatraemia, 42.5% of the patients had oral intake disorder, 22.3% of the patients were on loop diuretics, and 17.1% were on thiazide diuretics. Moreover, 1.2% of the patients had undergone TURP and 2.4% had undergone another procedure (Table II). The distribution of surgical procedures was: 13 major gastrointestinal system surgeries, 4 cardiovascular surgeries,

TABLE I. Main characteristics of the patients

Characteristic	<i>n</i> (%)
<i>Gender</i>	
Women	625 (53.5)
Men	546 (46.5)
<i>Presenting complaints</i>	
Dyspnoea	197 (16.8)
Nausea/vomiting	182 (15.5)
Abdominal pain	175 (14.9)
Altered level of consciousness	117 (10.0)
Other	98 (8.4)
Malaise	86 (7.3)
Fever	84 (7.2)
Dizziness	54 (4.6)
Chest pain	50 (4.3)
Lack of appetite	35 (3.0)
Reduced urine output	21 (1.8)
Seizures	21 (1.8)
Falls	20 (1.7)
Slurred speech	18 (1.5)
Syncope	13 (1.1)
<i>Chronic diseases</i>	
Hypertension	495 (42.3)
Diabetes mellitus	374 (31.9)
Cancer	263 (22.5)
Coronary artery disease	263 (22.5)
Heart failure	154 (13.2)
Chronic kidney disease	126 (10.8)
Cirrhosis	108 (9.2)
Chronic obstructive pulmonary disease (asthma)	91 (7.8)
Cerebrovascular disease	56 (4.8)
Epilepsy	42 (3.6)
Rheumatic disease	23 (2)
Arrhythmia	18 (1.5)
Psychiatric disease	13 (1.1)
Vascular disease	13 (1.1)
Inflammatory bowel disease	11 (0.9)
Hypothyroidism	11 (0.9)
Benign prostatic hyperplasia	11 (0.9)
Parkinson disease	10 (0.9)
Alzheimer/dementia	10 (0.9)
Other*	10 (0.9)
Anaemia	9 (0.8)
Hyperlipidaemia	9 (0.8)
Hepatitis	8 (0.7)
Heart valve disease	6 (0.5)
Multiple myeloma	4 (0.3)
Multiple sclerosis	4 (0.3)
Interstitial lung disease	3 (0.3)
Hyperthyroidism	3 (0.3)
Hydrocephalus	3 (0.3)
Myelodysplastic syndrome	3 (0.3)
Cardiomyopathy	2 (0.2)
Duchenne muscular dystrophy	2 (0.2)
Pulmonary embolism	2 (0.2)
<i>Serum osmolarity</i>	
Hypo-osmolar hyponatraemia	993 (84.8)
Iso-osmolar hyponatraemia	139 (11.9)
Hyperosmolar hyponatraemia	39 (3.3)

*Diseases included in the other category: portal hypertension, thrombotic thrombocytopenic purpura, adrenal insufficiency, encapsulated peritoneal sclerosis, Bartter syndrome, hypoparathyroidism, Budd-Chiari syndrome, arteriovenous malformation and tuberculosis were observed in 1 patient each (0.1%)

6 extremity surgeries, 4 cerebrospinal surgeries and 1 genitourinary surgery.

Comparison of the level of consciousness based on the mean sodium levels showed that those who were awake (A) had a higher mean sodium level than those who responded only to verbal (V) and painful (P) stimuli ($p < 0.001$; Table III). Of the patients included in the study, 61.8% had severe isolated hyponatraemia, whereas 38.2% had severe hyponatraemia coexisting with other disorders. In total, 6% of the patients had acute renal failure, 5.4% had decompensated heart failure and 5% had pneumonia (Table IV).

Considering the patient's distribution according to the emergency department end-points, we found that 53.1% of the patients were hospitalized. The intensive care hospitalization rate was 26.5%. The comparison of in-hospital mortality rates according to gender after the patients presented to the emergency department and were admitted to the hospital revealed that the mortality rate was higher among men ($p = 0.73$ and $p = 0.07$, respectively). The mortality rate of men was 12.8%.

The mean (SD) length of hospital stay was 9.6 (10.71) days. The mean (SD) hospital stay of discharged patients was 8.80 (9.71) days compared to 12.6 (13.41) days in deceased patients; this difference was statistically significant ($p < 0.001$).

The mean (SD) blood sodium levels were 120.27 (4.6) and 120.28 (4.85) in discharged and deceased patients, respectively ($p = 0.996$).

Considering the mortality in patients with chronic hyponatraemia according to the presence of chronic disease, we found that the mortality rate was higher in patients who had a history of cirrhosis and cancer and lower in patients who had a history of coronary artery disease ($p = 0.0002$, $p < 0.0001$ and $p = 0.04$, respectively; Table V).

TABLE II. Distribution of the factors that can cause hyponatraemia

Factor	n (%)
<i>Drugs</i>	
Loop diuretics	261 (22.3)
Thiazide diuretics	200 (17.1)
Potassium-sparing diuretics	138 (11.8)
Chemotherapeutics	79 (6.7)
NSAID	29 (2.45)
Carbamazepine	22 (1.9)
Fluoxetine	7 (0.6)
Haloperidol	4 (0.3)
Amitriptyline	1 (0.1)
<i>Presence of oral intake disorder</i>	498 (42.5)
<i>History of TURP</i>	14 (1.2)
<i>History of another procedure</i>	28 (2.4)
NSAID non-steroidal anti-inflammatory drug	TURP transurethral resection of prostate

TABLE III. Distribution of the level of consciousness according to mean sodium levels

Level of consciousness	n (%)	Mean (SD) sodium level
Alert	894 (76.3)	120.63 (4.12)
Verbal	138 (11.8)	119.23 (5.35)*
Pain	105 (9.0)	118.96 (5.55)*
Unresponsive	34 (2.9)	119.22 (8.26)

* $p < 0.001$

TABLE IV. Distribution of additional diagnoses and end-points at the emergency department

Item	n (%)
<i>Additional diagnosis</i>	
Acute renal failure	70 (6)
Decompensated heart failure	63 (5.4)
Pneumonia	58 (5)
Urinary tract infection	47 (4)
Sepsis	28 (2.4)
Hepatic encephalopathy	27 (2.3)
IADH syndrome	21 (1.8)
Diabetic ketoacidosis	16 (1.4)
Acute coronary syndrome	15 (1.3)
Pancreatitis	10 (0.9)
Peritonitis	9 (0.8)
Gastroenteritis	8 (0.7)
Epilepsy	7 (0.6)
Gastrointestinal bleeding	7 (0.6)
Arrhythmia	7 (0.6)
Intracranial haemorrhage	6 (0.5)
Cholangitis	6 (0.5)
Encephalitis	5 (0.4)
Ileus	4 (0.3)
Other*	33 (2.8)
<i>Emergency department end-points</i>	
Admission	622 (53.1)
Discharge	388 (33.1)
Referral	93 (7.9)
Discharge against medical advice	51 (4.4)
Death	17 (1.5)
<i>Hospital end-points</i>	
Discharge	489 (78.6)
Death	133 (21.4)

*Diseases included in the other category: ischaemic stroke and pulmonary embolism were observed in 3 patients each (0.3%). Intra-abdominal bleeding, deep vein thrombosis, ulcerative colitis attack, acute cholecystitis, neutropenic fever, splenic infarction were observed in 2 patients each (0.2%). hyperthyroidism, toxic hepatitis, diabetes insipidus, digoxin intoxication, committing suicide with drugs, pelvic abscess, extremity fracture, cellulitis, otitis media, Guillain-Barre syndrome, transplant rejection, uremic encephalopathy, Fournier gangrene, upper respiratory tract infection and newly diagnosed diabetes were observed in 1 patient each (0.1%) IADH inappropriate antidiuretic hormone

TABLE V. Distribution according to the presence of chronic disease and death

Chronic disease	No death (n=1021), n (%)	Death (n=150), n (%)	p value
Heart failure	135 (13.2)	19 (12.7)	0.85
Diabetes mellitus	336 (32.9)	38 (25.3)	0.06
Coronary artery disease	239 (23.4)	24 (16.0)	0.04
Cirrhosis	82 (8.0)	26 (17.3)	<0.001
Cancer	207 (20.3)	56 (37.3)	<0.001
Cerebrovascular disease	49 (4.8)	7 (4.7)	0.94
Chronic renal disease	116 (11.4)	10 (6.7)	0.08
Chronic obstructive pulmonary disease	77 (7.5)	14 (9.3)	0.44
Hypertension	442 (43.3)	53 (35.3)	0.07
Epilepsy	37 (3.6)	5 (3.3)	0.86

DISCUSSION

Severe hyponatraemia is associated with high morbidity and mortality.^{3,4} We investigated the demographic, aetiological and clinical characteristics of 1171 patients who had severe hyponatraemia. The prevalence of hyponatraemia was higher among women according to the previous studies.⁸⁻¹⁰ We too found this in our study (53.5% women). The patients were in the seventh decade of life, which is supportive of the literature. The mean age of women with severe hyponatraemia (69.1 [15.7] years) was higher than that of men (64.3 [14.0] years).

Hyponatraemia can manifest with variable clinical signs depending on the underlying cause and type of onset. Symptoms vary depending on the degree and rate of progression of hyponatraemia.¹¹ Patients may have symptoms such as vomiting and headache, and the clinical presentation may involve lethargy, psychosis, seizures, coma, respiratory arrest, brain stem herniation and death when there is deep and rapid progression of hyponatraemia.¹² There is a paucity of studies about the presenting complaints and symptoms in patients who report to the emergency department and have severe hyponatraemia at the emergency department. Balcý *et al.* reported that 14.7% of the patients presented to the emergency department with dyspnoea, 13.7% with fever and 11.9% with a systemic disorder.¹³ Olsson *et al.* reported that patients with severe hyponatraemia most commonly presented with neurological symptoms, fatigue, abdominal pain and dyspnoea.¹⁴ In our study 16.8% of the patients presented with dyspnoea, 15.5% with nausea/vomiting and 14.9% with abdominal pain.

According to previous studies on hyponatraemia, temperature changes lead to a change in the prevalence of hyponatraemia.¹⁵ In studies investigating the prevalence of seasonal hyponatraemia in patients admitted to the emergency department, it has been reported that most patients present during summer months, and this could be due to increased water intake in summers.¹² Contrary to previous studies, our study showed that 26.7% of the patients were admitted in winter. This can be attributed to Mersin being so hot in summer that older adults and those with a chronic disease leave Mersin during the summers.

Another study by Balcý *et al.* about the general characteristics of patients with electrolyte imbalance presenting to the emergency department reported that the most common electrolyte imbalance was hyponatraemia and the most common diseases were cancer, hypertension and diabetes mellitus at 39%, 30% and 20%, respectively.¹³ Turgutalp *et al.* conducted a study with patients aged 65 years and older who were hospitalized after admission in the emergency department and were found to have hyponatraemia. They reported that heart failure, diabetes mellitus, hypertension and Alzheimer disease were more common causes among very old patients.⁶ Another study by Brouns *et al.* with 91 patients having hyponatraemia reported that 34.1% of these patients had diabetes mellitus, 31.9% had cancer and 12.1% had heart failure.¹⁶ In our study, the distribution of chronic diseases was as follows: hypertension 42.3%, diabetes mellitus 31.9%, and cancer 22.5%. The use of diuretics for hypertension is a potential cause for hyponatraemia.

Chronic diseases and related multiple drug therapies are common in the elderly population. It has been reported that some of the prescribed drugs may have an adverse effect on water and food intake.⁶ Arampatzis *et al.* reported that hyponatraemia was more prevalent in patients who were on diuretics, and the concomitant use of different groups of

diuretics led to an increased prevalence of hyponatraemia. Another study conducted with patients with hyponatraemia showed that 14% of the patients were on loop diuretics, 12% were on thiazide diuretics, 6% were on aldosterone antagonists, and 1% were on potassium-sparing diuretics.¹⁷ Clayton *et al.* investigated the aetiology and outcomes in patients with severe hyponatraemia and reported that the aetiology was multifactorial and the most common causes were loop diuretics, thiazide diuretics and congestive heart failure, respectively. The same study also showed that treatment with thiazide diuretics was the most common cause of hyponatraemia in patients who had a single aetiology of hyponatraemia, and all patients who were on loop diuretics were found to have hyponatraemia with at least one more cause.¹⁸ In this study, 22.3% of the patients were on loop diuretics, 17.1% were on thiazide diuretics and 11.8% were on potassium-sparing diuretics. In this study, the fact that the aetiology of hyponatraemia was multifactorial and the existing chronic diseases of the patients caused hyponatraemia as well as the fact that loop diuretics were also frequently administered to treat congestive heart failure and cirrhosis could explain why loop diuretics were found to be the most common causative drugs for hyponatraemia.

Although TURP remains to be the preferred surgical treatment for benign prostatic hyperplasia, it constitutes a series of challenges associated with dilutional hyponatraemia, transurethral resection syndrome and haemorrhage.¹⁹ In this study, 1.2% of the patients had undergone TURP and 2.4% had undergone another procedure. Nausea and pain are strong ADH stimulants and cause syndrome of inappropriate antidiuretic hormone (SIADH) secretion in postoperative patients. Imbalances in sodium intake and loss are factors that predispose to hyponatraemia. Surgical procedures that may cause insufficient oral intake or increase the loss after the procedure and ADH release secondary to pain after the procedure were considered as factors that predispose to the development of hyponatraemia. Hypo-osmolar irrigation solutions are used in monopolar TURP, whereas bipolar TURP is performed in a normal saline medium.¹⁹ Monopolar circuit TURP using hypo-osmolar irrigation solutions is used in our hospital. That our patients had hyponatraemia secondary to TURP can be attributed to the use of hypotonic irrigation solutions.

It has been reported that an insufficient oral intake in older and very old patients is associated with the development of hyponatraemia and that the coexistence of oral intake disorder, vomiting and diarrhoea was the most common cause of hyponatraemia regardless of the severity, particularly in very old patients.⁶ Similar to the literature, our study showed that 42.5% of the patients had oral intake disorder. In normal conditions, the amount of sodium intake and excretion from the body is proportional. The main problem in hyponatraemia is the deterioration of body water balance. The inability to take water and salt due to the inability to eat and drink water, which we define as oral intake disorders, together with vomiting, diarrhoea, fever or water salt losses due to diuretic use may cause hyponatraemia.

Patients with hyponatraemia may have a broad spectrum of symptoms. The sudden onset of severe hyponatraemia may lead to brain damage, thereby causing symptoms associated with central nervous system dysfunction. Neurological symptoms have been reported when the sodium level decreases below 120 mEq/L.^{3,20} Olsson *et al.* reported that confusion/

disorientation, neurological symptoms (dysarthria, motor dysfunction, sensory losses, convulsions, vertigo, balance disorders and headache) and severe neurological symptoms (convulsions, coma) were more common in patients with serum sodium <120 mEq/L, but there was no statistically significant difference between the groups of varying severity of hyponatraemia.¹⁴ In our study, 10% of patients presented to the emergency department with an altered level of consciousness.

It has been reported that hyponatraemia, which is a marker of severe heart and liver disease, was frequently associated with malignancies, acute kidney injury, brain tumours and intracerebral haemorrhage.²¹ Ahamed *et al.* reported that 20.6% of the patients who had hyponatraemia were diagnosed with cardiac issues, 17.2% with respiratory issues, and 7.4% with gastrointestinal issues.²² Our study also showed that 61.8% of the patients had severe isolated hyponatraemia and 6% of the patients were diagnosed with acute kidney failure, 5.4% with decompensated heart failure and 5% with pneumonia.

Hyponatraemia is a condition associated with increased mortality and length of hospital stay depending on the comorbid chronic diseases and clinical conditions varying in severity based on the underlying cause and type of onset.¹¹ Lee *et al.* in 145 patients who had hyponatraemia reported that 2.8% of the patients died at the emergency department, 9.7% were discharged from the emergency department, 87.5% were hospitalized, and 17.3% of the hospitalized patients died at the hospital.²³ Another study by Naka *et al.* suggested that there was a strong relationship between hyponatraemia and mortality in hospitalized patients.²⁴ In our study, 53.1% of the patients were hospitalized and the mortality rate was 12.8%. Although the rates of discharge, hospitalization and death are different compared to the values reported in previous studies, our study supports the opinion that the mortality rate is high in hospitalized patients with hyponatremia.

Rao *et al.* found that the mortality rate associated with hyponatraemia was 9.09% in women and 33.3% in men with severe hyponatraemia, and the mortality rate was significantly higher in men.²⁵ Another study by Turgutalp *et al.* found no difference between gender in terms of mortality in patients with hyponatraemia.⁶ We also showed that the mortality rate was higher in men, but there was no statistically significant difference.

Hyponatraemia is associated with increased morbidity and mortality in patients with heart disease, kidney failure, cirrhosis and cancer.²⁶ Waikar *et al.* have reported that severe hyponatremia led to an increased risk of in-hospital mortality in patients with metastatic cancer and hepatic cirrhosis.¹¹ Clayton *et al.* studied patients who had severe hyponatremia and reported that those with congestive heart failure and liver disease had increased mortality.¹⁸ Another study by Klein *et al.* found that decreased serum sodium was an important predictor of the greater number of hospital days and increased 60-day mortality upon discharge in patients who were hospitalized due to heart failure and worsening systolic dysfunction.²⁷ Similar to the previous studies, our study also showed that the mortality rate was higher in patients with a history of cirrhosis and cancer and lower in patients with a history of coronary artery disease.

Different results have been reported in two previous studies on the relationship between serum sodium and mortality in patients with severe hyponatraemia. Lee *et al.*²³ have reported that lower serum sodium levels led to an increased mortality rate, whereas Chawla *et al.*²¹ have asserted that the mortality rate

increased at serum sodium levels between 120 and 124 and 125 mEq/L, but the trend was reversed and mortality rates started dropping at serum sodium levels below 120–125 mEq/L. We found no statistically significant difference between the mean sodium levels of the deceased and discharged patients.

Limitations

The study was retrospective, the duration of hyponatremia was not known, the patients could not be evaluated according to the volume, and clinical process including death could not be directly associated with serum sodium levels due to the presence of comorbid conditions in patients with severe hyponatraemia.

Conclusion

Our study showed that severe hyponatraemia was more prevalent in women and older patients, serum sodium levels were higher in conscious patients, and the mortality rate was higher in patients who had a history of cirrhosis and cancer. We also found that there was no significant difference between the mean sodium levels of the deceased and discharged patients who had severe hyponatraemia.

Conflicts of interest. None declared

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