



# Serum Sodium Levels in Patients with ST-Segment Elevation Myocardial Infarction: Its Effects on In-Hospital and Long-Term Clinical Outcomes

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## ABSTRACT

**Introduction:** There are some conflicting results in the association of serum sodium level with clinical outcomes in patients with acute myocardial infarction. The aim of this study was to investigate the effect of serum sodium levels on in-hospital and long-term outcomes in patients with ST-segment elevation myocardial infarction (STEMI).

**Patients and Methods:** A total of 1840 patients with STEMI (mean age  $57.3 \pm 11.8$ ; men 79.7%) who underwent primary percutaneous coronary intervention were included to the study. Baseline characteristics and outcomes were compared among the patients by admission serum sodium level and categorized accordingly; Q1, Q2, Q3 and Q4.

**Results:** There was not a significant difference regarding in-hospital mortality, cardiogenic shock, ventricular arrhythmia, acute kidney injury and major adverse cardiac events. Furthermore, after a follow-up period of 3-years; there was not a significant difference regarding long-term mortality and major adverse cardiac events.

**Conclusion:** In this large-scale study, we did not observe a significant association of serum sodium level with in-hospital and long-term clinical outcomes in patients with STEMI.

**Key Words:** Sodium; myocardial infarction, mortality.

## ST-Segment Yükselmeli Miyokardiyal Enfarktüsli Hastalarda Serum Sodyum Düzeyleri: Hastane İçi ve Uzun Dönem Klinik Sonuçları Üzerine Etkileri

### ÖZ

**Giriş:** Akut miyokardiyal enfarktüsli hastalarda serum sodyum düzeyleri ve klinik sonuçlar arasındaki ilişki ile ilgili çelişkili sonuçlar bulunmaktadır. Bu çalışmada, ST-segment yükselmeli miyokardiyal enfarktüsli (STYME) hastalarda serum sodyum düzeylerinin hastane içi ve uzun dönem klinik sonuçları üzerine etkileri araştırılmıştır.

**Hastalar ve Yöntem:** Primer perkütan koroner girişim uygulanan 1840 STYME hastası (ortalama yaş  $57.3 \pm 11.8$ ; erkek %79.7) çalışmaya dahil edilmiştir. Hastalar başvurudaki serum sodyum düzeylerine göre dört gruba ayrıldıktan sonra bazal karakteristik özellikleri ve klinik sonuçları karşılaştırılmıştır.

**Bulgular:** Hastane içi ölüm, kardiyojenik şok, ventriküler aritmi, akut böbrek hasarı ve majör kardiyak olaylar açısından belirgin farklılıklar bulunmamıştır. Ayrıca, üç yıllık takip sonrasında; uzun dönem ölüm ve majör kardiyak olaylar açısından benzer sonuçlar bulunmuştur.

**Sonuç:** Geniş ölçekli bu çalışmada, STYME olan hastaların serum sodyum düzeyleri ile hastane içi ve uzun dönem klinik sonuçlar arasında ciddi bir ilişki gözlenmemiştir.

**Anahtar Kelimeler:** Sodyum; miyokardiyal enfarktüs; mortalite.

## INTRODUCTION

Hyponatremia is recognized as the most common electrolyte disorder. It is a well-known predictor of poor prognosis in certain diseases such as congestive heart failure (CHF), chronic kidney disease, and liver cirrhosis<sup>(1-5)</sup>. In CHF, hyponatremia develops after excessive activation of baroreceptor-mediated hormones including arginine vasopressin (AVP), catecholamines and renin-angiotensin-aldosterone system based on low output rate. This hyponatremia process occurs in CHF after weeks. Moreover, recent studies showed that hyponatremia is a prognostic

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indicator in patients with acute myocardial infarction (AMI) (6-11). When we consider patients with ST-segment elevation myocardial infarction (STEMI) separately, especially compared to patients with myocardial infarction without ST-segment elevation; it consists of patients with generally low comorbidity and no significant electrolyte imbalance. The development of hyponatremia in these patients generally occurs due to CHF developing during follow-up or due to diuretic treatments. However, hyponatremia ( $> 130$  mg/dL), which is not as severe as in CHF, can be observed in some patients during admission. Studies analyzing STEMI patients, the relationship between in-hospital or admission sodium levels and in-hospital events are contradictory and it is still unclear whether hyponatremia has a direct effect on mortality and morbidity in STEMI patients, and previous studies on in-hospital survival in patients with hemodynamically stable have no enough information. The aim of this study was to investigate the effect of serum sodium levels on in-hospital and long-term outcomes in patients with ST-segment elevation myocardial infarction (STEMI).

## PATIENTS and METHODS

### Study Population

A total of 2094 consecutive patients who admitted to the emergency service of our tertiary heart center [annual percutaneous coronary intervention  $> 2500$ ] between January 2014 and December 2017 and who met criteria for STEMI were retrospectively evaluated. A total of 97 patients, who underwent thrombolytic therapy within the last 24 hours and with active infection, recent major surgical procedures or history of trauma, imaging modalities and investigational techniques for detecting systemic inflammatory disease, malignancy, or end-stage renal and liver failure, were excluded from the study. Moreover, 138 patients whose urea, glucose and/or sodium measurements were not studied within 8 hours after admission and 19 patients who did not come to follow-up were excluded from the study. A total of 1840 patients were included in the study. Our study was approved by the local ethics committee in accordance with the declaration of Helsinki.

Clinical, demographic, angiographic and laboratory parameters were taken from the hospital database. The sodium level of each patient was measured within the first 8 hours after admission. Serum sodium level was measured on Roche, Cobas 6000 Biochemistry Auto-Analyzer, USA. According to the sodium level, the patients were ranked from low to high and divided into 4 equal groups (quartile). In-hospital and long-term clinical events, evaluated by 2 independent observers, were compared between these 4 groups. In-hospital and long-term mortality was determined as the primary endpoint of the study.

In-hospital procedures such as primary PCI were performed by experienced interventional cardiologists. Primary PCI was usually performed via the femoral route. Echocardiographic imaging was performed on all patients within the first 12 hours after hospitalization, and left ventricular ejection fraction was measured by the Simpson method. During PCI, iodinated contrast agents with low osmolar content were used in all patients. In-hospital clinical events were evaluated and recorded by an experienced cardiologist. After PCI, patients were followed up in the coronary intensive care unit for observation. The estimated glomerular filtration rate was measured with the Cockcroft-Gault equation. In-hospital and follow-up medical treatments were planned in accordance with the guidelines of the European Society of Cardiology.

### Diagnostic Criteria in STEMI

Diagnostic criteria for STEMI are as follows: (a) Typical chest pain lasting more than 30 minutes and (b) with ST segment elevation in at least two leads, minimum 0.2 mV in men or 0.15 mV in women in V2-V3 leads and/or minimum 0.1 mV in other leads or newly developed definite or possible left bundle branch block. The right (V3R-V4R) and posterior (V7-V9) leads were obtained in the indication case<sup>(12)</sup>. Patients who admitted with STEMI within 12 hours from the onset of symptoms and underwent percutaneous coronary intervention (angioplasty and/or stent placement) were included in the study.

### Description of In-Hospital and Long-Term Events

*Cardiogenic shock*; defined as systolic blood pressure below 90 mmHg or vasopressor drug requirement to maintain systolic blood pressure above 90 mmHg and decrease in urine output or the presence of end-organ hypoperfusion results such as sweaty and cold extremities or fluctuation in mental state.

*Acute renal failure*; defined as a 0.5 mg/dL increase in serum creatinine concentration from baseline or a 50% decrease in creatinine clearance.

*Acute respiratory failure*; defined as a sudden deterioration in blood oxygenation ( $\text{PaO}_2 < 80$  mmHg or  $\text{SpO}_2 < 90$ ) and shortness of breath in the patient.

*Stent thrombosis*; defined as increase in biomarker levels after stent placement or a sudden onset of cardiac symptoms with ECG evidence of myocardial damage and the angiographic presence of a flow limiting thrombus within or 5 mm near previously placed stent.

*Revascularization*; defined as the decision of angioplasty procedure performed due to re-stenosis or occlusion in the infarct-related artery or CABG surgery.

*Recurrent MI*; defined as an increase in serum CK-MB levels, re-elevation in ST segments or dynamic ECG changes and an association of cardiac symptoms.

*Major cardiac event*; defined as cardiovascular death, recurrent MI and repeated target vessel revascularization (percutaneous or surgical).

### Statistical Analysis

Patients (n= 1840) were ranked by low to high sodium level and divided into quartiles with 4 equal numbers of patients (n= 460). The normality status of continuous variables was evaluated by Kolmogorov-Smirnov test. Continuous variables were shown in the table with mean and standard deviation values. The difference analysis of continuous variables with normal distribution was evaluated using ANOVA, and the difference analysis of variables without normal distribution was evaluated using Kruskal-Wallis test. The categorical variables were indicated as numbers and percentages, and the difference analysis was performed using Pearson's chi-square or Fisher's exact test. Out-of-hospital follow-up period was determined as 3 years. P value less than 0.05 was considered statistically significant. All analyzes were performed using SPSS 18.0 software (SPSS; IBM, Armonk, New York, USA).

## RESULTS

Basal characteristics of the patients and their values at the time of admission are summarized in Table 1. There was no difference between the groups in age, gender, body mass index, hypertension, diabetes mellitus, hyperlipidemia, smoking, chronic renal failure, previous MI frequency, systolic and diastolic blood pressures at the time of admission, heart rates, Killip classes, percutaneous intervention times and medical treatments. The rates of patients with anterior wall MI were similar, but the left ventricular EF of the patients in groups I and II was slightly lower. When we looked at the laboratory values at admission, the urea and creatinine values of the patients were similar. However, glucose levels of the patients were higher in groups 1 and 2. The patients were analyzed in 4 groups according to their serum sodium levels at admission. The mean sodium levels for group I were  $133.77 \pm 1.21$ ;  $136.54 \pm 0.58$  for group II;  $138.48 \pm 0.50$  for group III;  $141.27 \pm 1.64$  for group IV. When in-hospital events are analyzed; there was no statistically significant difference between the groups in cardiogenic shock, acute respiratory failure, acute renal failure, stent thrombosis, recurrent MI, major cardiac events and death.

When three-year long-term follow-up results of the patients were analyzed; there was no difference between the groups in stent thrombosis, recurrent MI, revascularization, major cardiac events and death from all causes.

## DISCUSSION

In this study; we divided 1840 STEMI patients into quartiles with 4 equal numbers of patients according to their sodium levels at the time of admission and analyzed as-hospital events and three-year follow-up. During the in-hospital period; No significant differences were found in death, cardiogenic shock, ventricular arrhythmia, acute kidney injury, and major cardiac events. Moreover, after 3 years of follow-up; similar results were found in long-term death and major cardiac events. Many factors were also identified such as advanced age, killip class of patient, delay in treatment, treatment strategy, history of MI, diabetes mellitus, renal failure, multiple vascular diseases and low left ventricular ejection fraction that affect the mortality of patients admitting with STEMI<sup>(13)</sup>.

The prognostic importance of hyponatremia in CHF was shown in many studies. The development of hyponatremia in CHF was explained by several mechanisms<sup>(12,14-17)</sup>. These are vasopressin secretion, carotid baroreceptor activation and hypothalamus stimulation that can take 1-2 weeks. STEMI is an acute event. It seems unlikely to be significant hyponatremia (< 130 mg/dL) at the beginning.

When we analyze the studies on sodium levels of STEMI patients, the results are controversial and there is no effect of causes other than sodium for results. In the studies, patients with hyponatremia constitute very little part of the general STEMI patients and this leads to a serious difference in the number of patients in these groups. Goldberg et al. included patients who developed hyponatremia at the time of admission and follow-up in the study. In the study, hyponatremia was defined as an indicator of 30-day mortality<sup>(18)</sup>. Most patients underwent fibrinolytic therapy and this does not reflect the current age of primary percutaneous intervention. These treatments may be responsible for the poor outcome and developing CHF in these patients. Moreover, a significant rate of patients with hyponatremia is diabetic and involved in the high admission killip class. It seems that the main cause of the mortality of the patients in this hyponatremia group is the patient's clinic. In the study including the long-term results of hyponatremia by Goldberg et al.; for the same reasons, the results of the study are affected by factors other than hyponatremia such as diabetes mellitus and high admission killip class<sup>(19)</sup>.

Klopotowski et al. stated in their study that hyponatremia increased in-hospital mortality<sup>(11)</sup>. However, in this study; only 96 of 1858 STEMI patients were in the hyponatremia group. No statistically significant difference was found in the group statistics made by dividing into quantile.

In the study of Bozbay et al., it was stated that hyponatremia increased mortality<sup>(20)</sup>. The number of patients in the study (366

**Table 1. Baseline characteristics and clinical results of patients classified according to serum sodium levels**

	Serum sodium level at admission, mosmol/kg (n= 1840)				P
	I (n= 460)	II (n= 460)	III (n= 460)	IV (n= 460)	
Age	57.6 ± 12.1	57.7 ± 11.8	56.6 ± 11.7	57.6 ± 12.0	0.519
Male gender	369 (80.2)	380 (82.6)	380 (82.6)	354 (77.0)	0.097
Body mass index	27.2 ± 3.9	27.5 ± 3.9	27.3 ± 3.9	27.6 ± 3.7	0.268
History					
Hypertension	132 (28.7)	146 (31.7)	137 (29.8)	148 (32.2)	0.626
Diabetes mellitus	147 (32.0)	130 (28.3)	109 (23.7)	98 (21.3)	0.001
Hyperlipidemia	89 (19.3)	90 (19.6)	98 (21.3)	87 (18.9)	0.811
Smoking	164 (35.7)	154 (33.5)	164 (35.7)	166 (36.1)	0.840
Previous MI	71 (15.4)	64 (13.9)	59 (12.8)	73 (15.9)	0.535
Previous PCI	64 (13.9)	58 (12.6)	51 (11.1)	66 (14.3)	0.452
Previous bypass	13 (2.8)	9 (2.0)	4 (0.9)	15 (3.3)	0.070
Chronic kidney disease	22 (4.8)	23 (5.0)	18 (3.9)	26 (5.7)	0.672
Admission time					
Systolic blood pressure (mmHg)	131.9 ± 24.2	129.8 ± 25.1	131.9 ± 25.7	132.4 ± 25.6	0.381
Diastolic blood pressure (mmHg)	73.5 ± 14.4	73.3 ± 14.1	74.3 ± 14.1	74.0 ± 14.7	0.680
Heart rate (beats/minute)	78 ± 15	78 ± 15	78 ± 15	79 ± 16	0.979
Killip classification	1.11 ± 0.53	1.13 ± 0.57	1.10 ± 0.50	1.11 ± 0.53	0.900
Left ventricular ejection fraction (%)	46.6 ± 10.5	48.0 ± 10.3	49.0 ± 10.0	48.8 ± 10.8	0.007
Front wall MI	223 (48.5)	199 (43.3)	220 (47.8)	215 (46.7)	0.392
Chest pain duration (hours)	7.2 ± 5.7	7.3 ± 5.7	7.6 ± 5.7	7.1 ± 5.7	0.623
Pain-balloon time (hour)	7.5 ± 5.7	7.7 ± 5.7	7.6 ± 5.7	7.1 ± 5.7	0.608
Door-to-balloon time (minutes)	19.5 ± 9.3	20.3 ± 9.9	20.2 ± 10.3	19.8 ± 9.7	0.620
Laboratory variables at admission					
Admission time KK-MB (ng/mL)					< 0.001
Peak creatine kinase-MB (ng/mL)	110.0 ± 123.3	107.4 ± 132.6	88.6 ± 97.7	80.1 ± 114.7	< 0.001
Glucose (mg/dL)	175.0 ± 88.7	164.0 ± 75.7	144.3 ± 55.8	135.7 ± 52.4	< 0.001
Creatinine (mg/dL)	0.93 ± 0.48	0.90 ± 0.37	0.89 ± 0.32	0.93 ± 0.34	0.234
tGFO (mL/min/1.73 m <sup>2</sup> )	110.8 ± 41.6	112.1 ± 38.9	112.2 ± 36.8	106.6 ± 39.8	0.108
White blood cell count (cells/ $\mu$ L)	12.4 ± 4.4	11.9 ± 3.8	11.6 ± 3.8	11.1 ± 3.9	< 0.001
Hematocrit (%)	40.0 ± 15.0	78.6 ± 15.3	78.8 ± 15.1	79.0 ± 16.0	< 0.001
Blood urea nitrogen (mg/dL)	17.4 ± 7.9	17.3 ± 6.3	17.1 ± 6.3	17.2 ± 5.8	0.146
Vascular disease (stenosis> 50%)					
1-vessel	300 (65.2)	262 (57.0)	296 (64.3)	261 (56.7)	0.007
2-vessel	85 (18.5)	114 (24.8)	87 (18.9)	115 (25.0)	0.016
3-vessel	75 (16.3)	84 (18.3)	77 (16.7)	84 (18.3)	0.802
PCI type					
Only PTCA	69 (15.0)	59 (12.8)	58 (12.6)	60 (13.0)	0.695
Only stent	58 (12.6)	66 (14.3)	71 (15.4)	57 (12.4)	0.482
PTCA and Stent	284 (61.7)	253 (55.0)	244 (53.0)	228 (49.6)	0.002

**Table 1. Baseline characteristics and clinical results of patients classified according to serum sodium levels (continues)**

	Serum sodium level at admission, mosmol/kg (n= 1840)				P
	I (n= 460)	II (n= 460)	III (n= 460)	IV (n= 460)	
Out of hospital medication					
B-blocker	397 (86.3)	405 (88.0)	394 (85.7)	406 (88.3)	0.567
Statin	400 (87.0)	405 (88.0)	406 (88.3)	399 (86.7)	0.865
Diuretic	28 (6.1)	37 (8.0)	44 (9.6)	40 (8.7)	0.256
ADEI or ARB	428 (93.0)	438 (95.2)	429 (93.3)	430 (93.5)	0.507
Oral antihyperglycemic agents	162 (35.2)	173 (37.6)	168 (36.5)	164 (35.7)	0.881
Insulin therapy	144 (31.3)	135 (29.3)	140 (30.4)	157 (34.1)	0.442
In-hospital period					
Cardiogenic shock	30 (6.5)	29 (6.3)	23 (5.0)	25 (5.4)	0.729
Acute respiratory failure	20 (4.3)	23 (5.0)	19 (4.1)	21 (4.6)	0.932
Acute kidney injury	56 (12.2)	68 (14.8)	51 (11.1)	44 (9.6)	0.095
Ventricular arrhythmia	23 (5.0)	24 (5.2)	32 (7.0)	43 (9.3)	0.029
Stent thrombosis	5 (1.1)	9 (2.0)	15 (3.3)	13 (2.8)	0.124
Recurrent MI	5 (1.1)	10 (2.2)	13 (2.8)	14 (3.0)	0.189
Revascularization	11 (2.4)	31 (6.7)	31 (6.7)	30 (6.5)	0.008
Major cardiac events	29 (6.3)	45 (9.8)	38 (8.3)	49 (10.7)	0.099
Death	24 (5.2)	29 (5.3)	24 (5.2)	26 (5.7)	0.876
Out-of-hospital period					
Time to follow up (months)					
Stent thrombosis	18 (3.9)	21 (4.6)	28 (6.1)	22 (4.8)	0.477
Recurrent MI	29 (6.3)	32 (7.0)	32 (7.0)	32 (7.0)	0.972
Revascularization	33 (7.2)	54 (11.7)	49 (10.7)	47 (10.2)	0.117
Major cardiac events	58 (12.6)	65 (14.1)	56 (12.2)	63 (13.7)	0.799
Death due to all causes	36 (7.8)	33 (7.2)	36 (7.8)	40 (8.7)	0.863

Continuous variables are presented as mean ± SD; nominal variables presented as frequency (%).

patients) is low and the number of patients with hyponatremia (56 patients) constitutes approximately 15% of the patients incompatible with the literature. The hyponatremia group also consists of older patients. It is known that advanced age is associated with mortality in patients with STEMI<sup>(13)</sup>. It is contradictory that it was not found an independent determinant although patients over 65 years of age had 6 times more mortality in this study. The fact that important laboratory values such as creatinine were not examined for independent determinants is an important deficiency of this study. Tatlısu et al. calculated the plasma osmolality of 3748 STEMI patients<sup>(21)</sup>. They found that high plasma osmolality was associated with in-hospital and long-term mortality. In the same study, when fasting glucose and blood urea nitrogen, which are a part of plasma osmolality, were analyzed separately, it was found to be associated with

mortality; while sodium was not associated with mortality in this large-scale study in compatible with our study.

Our study has some limitations. First, it is a single center and retrospective observational study. Our study includes only patients with STEMI and this does not cover all patients with AMI. Besides, the instantaneous value of sodium at admission was used for statistical analysis and changes that could be observed during follow-up were ignored.

Consequently; when we analyzed the patients in this study by dividing the number of patients equally into quantiles according to the reference sodium level; we did not find that the admission sodium value is associated with in-hospital and 3-year mortality. When we compared STEMI patients with MI patients without ST elevation, they are patients with less

comorbidity and less routine blood values. In our study, patients who firstly admitted with STEMI constitute approximately 80% of the patients. Therefore, the patients in our study are also patients with less comorbid diseases and there is no severe hyponatremia in the sodium values of the patients. Hyponatremia is associated with mortality in chronic heart failure in patients with chronic ischemic heart disease and the time is required for the development of specific hyponatremia. STEMI is an acute event and patients are intervened early in the age of primary percutaneous intervention.

**Ethics Committee Approval:** The study was approved by the Kartal Dr. Lutfi Kırdar City Hospital Clinical Research Ethics Committee (Decision no: 514/196/5; Date: 24.02.2021).

**Informed Consent:** Informed consent was obtained.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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