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Original Article

Effect of serum osmolality on 6-year survival rates in patients with acute myocardial infarction

Akut miyokard enfarktüsü geçiren hastalarda serum osmolalitesinin 6 yıllık sağkalım oranlarına etkisi

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Abstract

Aim: In the present study, we aimed to evaluate the potential relationship between serum osmolality and mortality rates in a six year of follow-up in patients with a history of acute myocardial infarction.

Material and Methods: A retrospective study was designed. Participants were the patients with a first attack AMI, who were referred to our tertiary referral center for angiography. The relationship between the biochemical values of patients who were hospitalized between the period January 2008 - June 2009 and their survival in six years was investigated. Clinical variables of baseline characteristics, in-hospital management, and in-hospital adverse outcomes were recorded.

Results: Two hundred and four patients, 174 men (85%) and 30 women (15%), were included in the study. Median serum osmolality was 295.87 mOsm/kg. Mean follow-up time was 61.31±1.68 months. The best cut-off value of the plasma osmolality to predict the 6-year mortality was 303.94 mOsmol/kg.

Conclusion: The higher the osmolality, the worse the six-year survival is in patients with first episode AMI even in the absence of diabetes mellitus and chronic kidney disease. We believe that hyperosmolality can be targeted in treatment and prevention efforts as well as its use when evaluating outcomes of the cardiac diseases.

Keywords: cardiac risk; chronic kidney disease; cut-off point; mortality; osmolality

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Öz

Amaç: Bu çalışmada akut miyokard enfarktüsü öyküsü olan hastalarda altı yıllık takipte serum osmolalite ve mortalite oranları arasındaki potansiyel ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Retrospektif bir çalışma tasarlandı. Katılımcılar, anjiyografi için üçüncü basamak sevk merkezimize yönlendirilen, ilk atak AMI atağı olan hastalardı. Ocak 2008 - Haziran 2009 arasında yatan hastaların biyokimyasal değerleri ile altı yıl içinde hayatta kalmaları arasındaki ilişki araştırıldı. Başlangıç özellikleri, hastane içi yönetim ve hastane içi olumsuz sonuçların klinik değişkenleri kaydedildi.

Bulgular: İki yüz dört hasta, 174 erkek (% 85) ve 30 kadın (% 15) çalışmaya dahil edildi. Ortalama serum osmolalitesi 295.87 mOsm / kg idi. Ortalama takip süresi 61.31 ± 1.68 ay idi. Plazma osmolalitesinin 6 yıllık mortaliteyi tahmin etmek için en iyi kesme değeri 303.94 mOsmol / kg idi.

Sonuç: Osmolalite ne kadar yüksek olursa, diyabetes mellitus ve kronik böbrek hastalığı olmasa bile ilk atak AMI'si olan hastalarda altı yıllık sağkalım daha kötüdür. Hiperosmolalitenin, kalp hastalıklarının sonuçlarını değerlendirirken kullanımının yanı sıra tedavi ve önleme çabalarına da hedeflenebileceğine inanıyoruz.

Anahtar kelimeler: kardiyak risk; kronik böbrek hastalığı; kesme noktası; mortalite; ozmolalite

Introduction

Cardiovascular diseases including coronary artery disease, acute myocardial infarction, and heart failure is the leading cause of mortality worldwide (1,2).

Increased serum osmolality is considered a risk for coronary artery disease (3,4). The presence and severity of coronary artery disease confirmed by angiography was found to be related with the serum osmolality (5).The negative effect of diabetes mellitus, renal insufficiency and both hyponatremia and hypernatremia on coronary arteries is well documented and they have long been known as a risk factor for coronary artery disease (6-9).

Osmolality is a useful marker of hydration status and it can be calculated using fasting blood glucose, blood urea nitrogen (BUN) and sodium (Na) values (5,10,11).Studies suggested that in patients presenting with Acute Myocardial Infarction (AMI), hyperglycemia at admission is associated with increased mortality (12,13).Moreover, the relationship between impaired renal function and long-term mortality is well established (14). And, elevated BUN level is highly predictive of mortality, independent of creatinine in a heterogeneous critically ill population (15). In the literature a limited number of sources have shown the relationship of serum osmolality with mortality (16,17).

In the present study, we aimed to assess serum osmolality in patients with AMI; to evaluate the potential relationships between other biochemical factors and mortality rates in a six year of follow-up.

Material and Methods

A retrospective study of 204 patients with a first attack AMI, who were referred to our tertiary referral centre for angiography between the period January 2008 - June 2009 were included; informed consent was not assumed necessary because of the retrospective observational nature of the study and all steps were taken to ensure the anonymity of the data. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Definition of AMI is made when there is a rise /fall of cardiac biomarkers, with the evidence of symptoms, suggestive electrocardiographic changes, or imaging evidence of new loss of viable myocardium or regional abnormality of wall motion (18).

Exclusion criteria are anemia, alcohol intake in 24 hours, acute infections, recent major trauma, systemic inflammatory disease, cancer, and end-stage kidney disease.

The relationship between the biochemical values of patients who were hospitalized in 2010 and their survival over the past 6 years were investigated. Clinical variables of baseline characteristics, in-hospital management and in-hospital adverse outcomes were recorded. Mortality was evaluated by hospital records and follow-up interviews by consecutive telephone contacts. Laboratory results, clinical characteristics, cardiovascular risk factors, co-morbidities, coronary morphology, and medication at hospital discharge were noted for all patients. The authors collecting the data did not interfere with the management process.

Complete blood cells were analyzed in an automated hematology analysis system (Coulter LH-780 hematology analyzer; Beckman Coulter Inc., Fullerton, CA, USA) which measures platelet size and platelet count using aperture-impedance technology. Fasting Blood Glucose, BUN, Sodium, Potassium, Creatinine, AST, ALT, T Chol, HDL, Tg, GGT, Uric acid were analyzed using commercial kits with auto-analyzer (ADVIA® 2400 Clinical Chemistry System, Siemens, USA).

Plasma osmolality at admission were calculated with the following formula:

Osmolality = 1.86×sodium mmol/l + (glucose mg/dl/18) + (BUN mg/ dl/2.8) + 9

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

Descriptive statistics were reported as mean±standard deviation for normally distributed variables, median (min-max) for not normally distributed variables and frequency and percentage for categorical variables. One-way ANOVA, Kruskal Wallis, Pearson chi-square Fisher Freeman Halton tests were used to compare osmolality groups. The log-rank test was used to determine the difference between Kaplan-Meier curves for survival time and mean survival time was reported. To determine the prognostic factors that affect overall survival time Cox proportional hazard regression analysis with backward selection procedure was performed and results of the final step was reported. Results were reported as hazard ratios with 95% confidence intervals (CI) and related p-values. Receiver operating characteristic curve analysis was used to assess the ability of the plasma osmolality to predict the 6-year mortality. $p<0.05$ was considered statistically significant. IBM SPSS v.20 was used for statistical analysis.

Results

Two hundred and four patients, 174 men (85%) and 30 women (15%), were included in the study. The mean age of participants was 58.60±9.86. Median serum osmolality was 295.87(269.54-358.41) mOsm/kg. Patients were divided based on osmolality into low (<285, n=26), normal (285 to 300, n=103), and high (>300, n=75) groups.

Age, hypertension and presence of diabetes mellitus were associated with high osmolality but smoking was not associated with osmolality (Table1).

Use of drugs containing Angiotensin Converting Enzyme (ACE) inhibitor, acetylsalicylic acid (ASA), Statins and Oral Antidiabetic Drugs was also associated with high osmolality (Table2).

Mean follow-up time was 61.31±1.68 months. Sixteen cases died while in hospital. In total, 25 cases died within 1 year, 28 cases within 2 years, 32 cases within 3 years, 34 cases within 4 years, 36 cases within 5 years and 38 cases within 6 years. Of the 16 deaths in the hospital, 15 were in the group with high osmolality (> 300 mOsm). Similarly, in the following years mortality was higher in the group with higher osmolality. In the high osmolality group, heart rate was higher in this group and the mean blood pressure was lower than the other groups. In addition, high osmolality was associated with rales, stable angina pectoris presence and low ejection fraction. Number of effected vessels increased with high osmolality (Table3).

High osmolality was associated with hemogram and biochemical parameters (Table4). Fasting glucose level, BUN and sodium are the parameters we calculated the osmolality in the formula. In addition, creatinine, AST, ALT, total cholesterol, LDL and uric acid were associated with osmolality. Hemoglobin decreased with high osmolality, but WBC increased with high osmolality. Platelet count was the highest in the normal osmolality group. Sedimentation and cardiac biomarkers were high in the group with high osmolality. Hs-CRP values were more than 5-fold higher in the high osmolality group than in the other groups.

Osmolality and Hs-CRP were considered for cox regression, moderate osmolality was found protective factor and reduced death risk %87.10 (p=0.007). Hs-CRP was found as a risk factor and one unit increase in Hs-CRP will increase death risk 1.02 time (p=0.002).

Kaplan Meier analysis results showed high osmolality was associated with decreased mortality compared with low or normal osmolality (p=0.001). In addition sodium and fasting blood glucose values were also associated with mortality (p=0.031 and p<0.001 respectively) (Table5 and Figure1).

Table 6 demonstrates cox regression analysis results of the patients (n=181) for mortality, excluding the patients with a history of diabetes mellitus and chronic kidney disease (n=23). BMI> 25 was defined as a risk factor for 6-year mortality. In the case of BMI> 25, the risk of mortality was 3.01 times greater.

Table 1. Baseline characteristics by osmolality groups

	<285mOsm (n=26)	285-300 mOsm (n=103)	>300 mOsm (n=75)	p-value
Age (years)	53.23±7.53	57.04±9.68	62.60±9.41	<0.001
Gender (Female/Male)	5/21	14/89	14/61	0.598
BMI (kg/m2)	26.38(21.55-30.09)	25.95(18.49-32.01)	25.40 (21.01-30.12)	0.285
Waist Circumference	91 (74-112)	92 (60-119)	90 (68-121)	0.202
Hypertension	7 (26.90%)	18 (17.50%)	31 (41.30%)	0.002
Diabetes Mellitus	5 (19.20%)	19 (18.40%)	28 (37.30%)	0.012
Smoking Habits	16 (61.50%)	65 (63.10%)	43 (57.30%)	0.736

Data were presented as mean ± st. deviation, median (min.-max.) and n(%).

Table 2. Osmolality and the drugs used by the participants

	<285mOsm (n=26)	285-300 mOsm (n=103)	>300 mOsm (n=75)	p-value
ACE Inhibitors	4 (15.40%)	12 (11.70%)	20 (26.70%)	0.033
ASA	5 (19.20%)	23 (22.30%)	30 (40%)	0.019
Beta-blockers	1 (3.80%)	9 (8.70%)	12 (26%)	0.144
Statins	3 (11.50%)	7 (6.80%)	16 (21.30%)	0.016
Nitrates	1 (3.80%)	6 (5.80%)	8 (10.70%)	0.362
Oral Antidiabetic Drugs	3 (11.50%)	11 (10.70%)	23 (30.70%)	0.002
Insulin	2 (7.70%)	6 (5.80%)	12 (16%)	0.073

Angiotensin Converting Enzyme (ACE), Acetylsalicylic Acid (ASA), Data were presented as n (%)

Table 3. The relationship between serum osmolality and some cardiac parameters

	<285 mOsm (n=26)	285-300 mOsm (n=103)	>300 mOsm (n=75)	p-value
Congestive Heart Disease	1(3.80%)	0	6(8%)	0.007
Mean Blood Pressure	100(45-130)	90(45-150)	80(30-150)	0.004
Heart Rate	68.50(54-121)	72(30-111)	80(30-122)	0.016
Rales	1(3.80%)	2(1.90%)	25(33.30%)	<0.001
Stable Angina Pectoris	4(15.40%)	25(24.30%)	32(42.70%)	0.006
Ejection Fraction(on admission)	45(30-60)	45(35-60)	40(20-55)	<0.001
Vessel occlusion (%)	100(80-100)	99(30-100)	98(60-100)	0.433
Number of effected vessels	1.50(1-3)	2(1-3)	2(1-3)	0.048
Intervention				
pPCI	25(96.20%)	81(78.60%)	64(85.30%)	
CABG	0	17(16.50%)	5(6.70%)	0.058
Medical Treatment	1(3.80%)	5(4.90%)	6(8%)	
Stent needed	25(96.20%)	83(80.60%)	64(85.30%)	0.142
Stent length	16(0-69)	16(0-42)	18(0-46)	0.056
Stent diameter	3(0-4)	3(0-4)	3(0-4)	0.335
Residual occlusion	2(7.70%)	14(13.60%)	18(24%)	0.078
In-hospital mortality	0	1(1%)	15(20%)	<0.001

pPCI: primary percutaneous coronary intervention, CABG: coronary artery bypass grafting, Data were presented as median(min.-max.) and n(%).

Table 4. Osmolality and laboratory findings

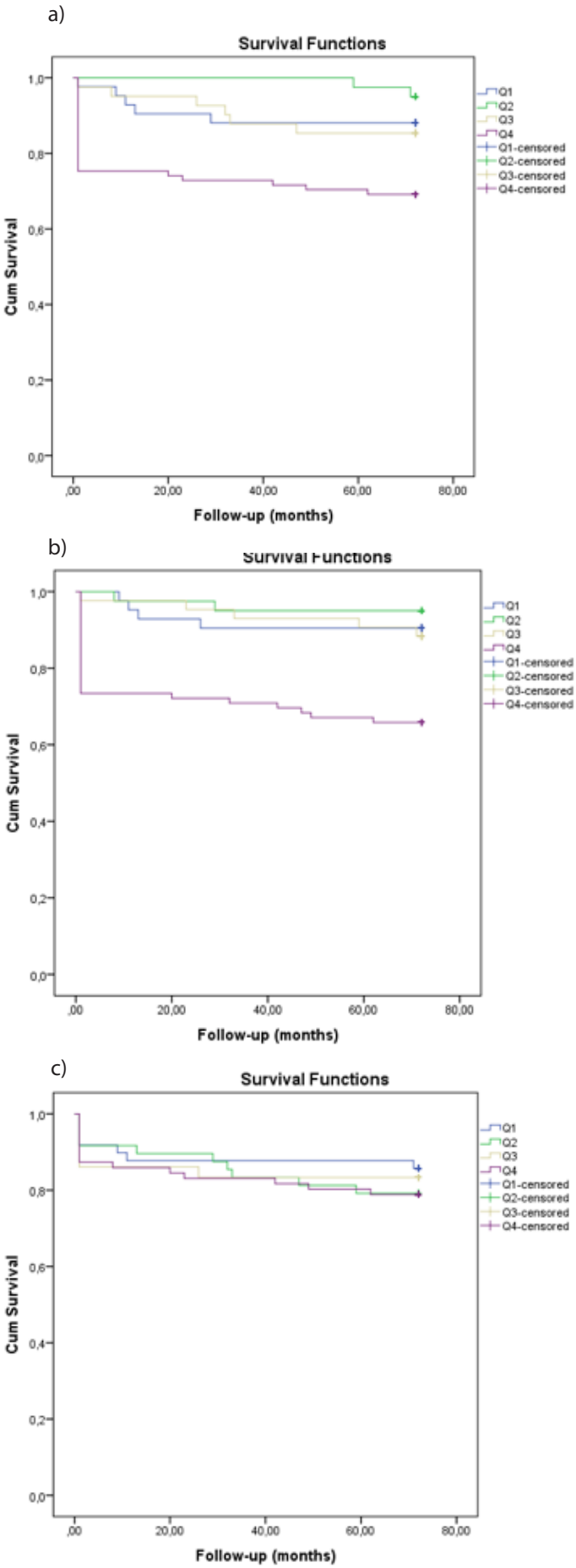
	<285 mOsm (n=26)	285-300 mOsm (n=103)	>300 mOsm (n=75)	p-value
Fasting Blood Glucose	101.50(78-163)	108(72-194)	113(72-210)	0.003
Blood Urea Nitrogen	20.50(16-72)	23(13-58)	41(16-190)	<0.001
Sodium	133.50(119-136)	138(133-143)	143(135-153)	<0.001
Potassium	4.20(3.30-5.70)	4(3.30-5.70)	3.90(3.10-5.60)	0.083
Creatinine	0.71(0.45-2.10)	0.75(0.40-1.70)	1.02(0.40-6.14)	<0.001
AST	165.50(11-698)	152(19-421)	198(16-1544)	0.001
ALT	60(7-320)	48(10-178)	81(8-511)	<0.001
Total Cholesterol	184.69±30.36	189.83±31.47	169.93±37.42	0.001
LDL	115.50(62-174)	121(60-205)	100(54-172)	0.002
HDL	33(19-47)	34(23-51)	33(17-62)	0.292
Triglycerides	145.50(62-464)	148(39-351)	130(42-302)	0.188
GGT	28.40(13-87)	28.25(8.90-161)	31(7.80-188)	0.135
Uric acid	5(2.90-7)	5.04(2-12.20)	5.50(1.85-17)	0.005
Hemoglobin	13.20(11.30-14.80)	13.40(7.90-15.60)	12.50(9.10-120)	0.001
White Blood Cell	11.35(6.90-18.10)	10.50(5.80-18)	14(5.80-21.60)	<0.001
Neutrophile	7.95(4.20-13.70)	6.90(3.20-13.80)	9.40(3.10-16.70)	<0.001
Monocyte	0.43(0.20-1)	0.41(0.14-1.10)	0.60(0.20-2.20)	0.007
Lymphocyte	2.35(1.30-3.42)	2.30(1.10-4.10)	2.80(0.90-4)	0.063
Platelets	292.08±76.02	311.43±81.38	269.95±80.81	0.004
PDW	13.49±1.20	13.21±1.43	13.21±1.39	0.642
RDW	14(11.80-18.10)	13.80(9.60-19.80)	14.10(11-114.40)	0.566
MPV	8.69±0.81	8.43±0.93	8.69±0.99	0.184
Sedimentation	19.50(3-64)	21(4-68)	38(4-94)	<0.001
hs-CRP	3.05(0.20-36.60)	3(0.05-119)	17(0.63-112)	<0.001
CK-MB	54(11-566)	49(9-417)	81(8-455)	0.001
Troponine	1.25(0.01-96)	1.80(0.01-100)	3.30(0.02-100)	0.013

Data were presented as mean ± st. deviation, median (min.-max.) and n (%).

Table 5. Kaplan-Meier analysis results

Risk Factor		Number of patients at risk (%)	Number of events (%)	Duration of Survival in Months	p-value
Osmolality					
	<285	26(12.70%)	1(3.80%)	69.27	
	285-300	103(50.50%)	2(1.90%)	70.62	<0.001
	>300	75(36.80%)	19(25.30%)	54.01	
Sodium					
	≤145	178(87.30%)	16(9%)	65.62	
	>145	26(12.70%)	6(23.10%)	55.62	
Fasting Blood Glucose					
	≤125	148(72.50%)	6(4.10%)	69.12	
	>125	56(27.50%)	16(28.60%)	51.71	<0.001

Analysis for BUN couldn't be performed because of the small number of the cases



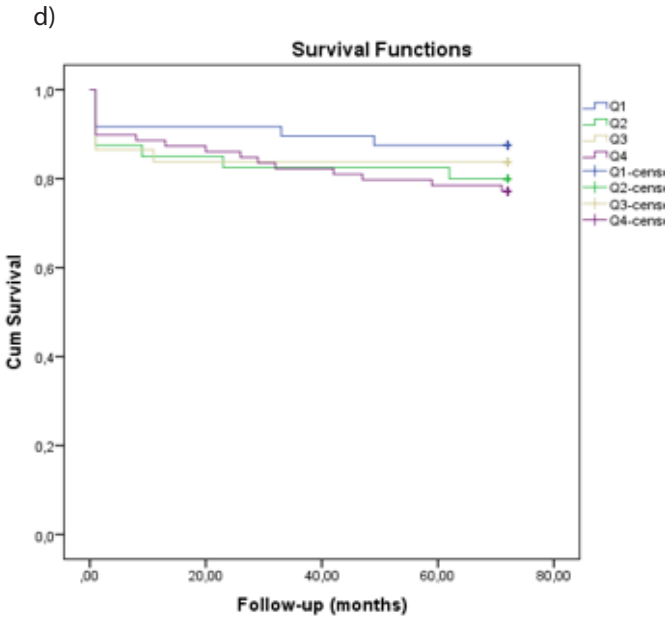


Figure 1. *Kaplan–Meier curve for overall survival in patients with a first attack acute myocardial infarction (n =204) stratified by admission plasma osmolality (a), bun (b), sodium (c), and fasting blood glucose (d) levels, respectively. Cum, cumulative; Q, quartile.*

Table 6. Cox Regression analysis results for mortality

Variable	B	HR(95%CI)	p-value
BMI (ref. cath.:≤25)	1.10	3.01(0.86:10.47)	0.084
Sodium (ref. cath.: >145)	2.07	7.95(1.96:32.23)	0.004
Hypertension (ref. cat.: YOK)	1.15	3.16(1.10:9.08)	0.032
Troponin on admission	-0.03	0.97(0.94:0.99)	0.047
CK-MB on admission	0.01	1.01(1.01:1.06)	<0.001
Osmolality	0.08	1.08(1.05:1.11)	<0.001

Cox regresyon model significance (p<0.001); BMI: Body mass index; ref.cath: referans cathegory

Sodium level >145 was defined as a risk factor for 6-year mortality. If the sodium level was >145, the risk of mortality was 7.95 times more than if it was ≤145. Hypertension was defined as a risk factor for 6-year mortality. The risk of mortality was 3.16 times higher in case of hypertension.

After receiver operating characteristic curve analysis, the best cut-off value of the plasma osmolality to predict the in-hospital mortality was 303.94 mOsmol/kg with 57% sensitivity and 83% specificity (area under the curve: 0.719; 95% CI: 0.615–0.823; p<0.001) (Figure 2).

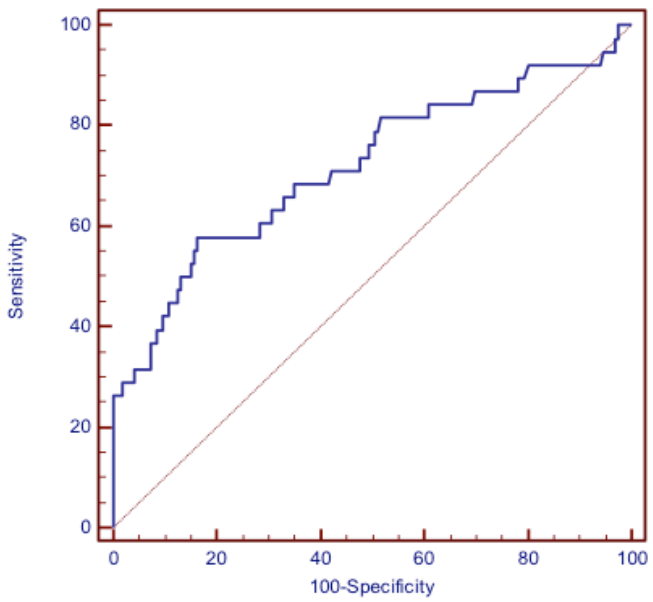


Figure 2. *Receiver operating characteristic curve analysis showed that the best cutoff value of the plasma osmolality to predict the 6 years mortality was 303.94 mOsmol/kg with 57% sensitivity and 83% specificity. AUC=0.719; 95% CI 0.625-0.823; p<0.001.*

Discussion

The present study demonstrated us that osmolality increases the mortality risk in patients without a history of diabetes mellitus and chronic kidney disease. Previous studies suggested that osmolality is a risk factor for mortality (16, 17, 19) but the risk might be originated from concomitant renal insufficiency. We have shown that six year survival was better in patients with lower osmolality even in the absence of diabetes mellitus or chronic kidney disease.

Moderate osmolality was found as a protective factor and it resulted in a reduced death risk. In a recent study by Tatlisu et al. investigated the association of plasma osmolality with all-cause mortality in ST-segment elevation in 3748 myocardial infarction patients treated with a primary percutaneous coronary intervention (19). They followed of patients for a mean period of 22 months and found that plasma osmolality was a predictor of both in-hospital and long-term all-cause mortality. They found that patients with higher plasma osmolality had 3.7 times higher long-term all-cause mortality rates than patients with lower plasma osmolality. In the present study, the patients with a first attack AMI followed up for six years. The patients with the highest osmolality values had a poor prognosis in both studies. The underlying mechanisms that influence osmolality and its trajectory are likely related to neuro-hormonal abnormalities.

White blood cell, neutrophile count, monocyte count, and lymphocyte count were higher in high osmolality group while hemoglobin levels were low. Rasouli et al. found that indicators of dehydration and haemoconcentration are associated with coronary artery disease and its severity. In that study, white blood cells and its subgroups and hemoglobin levels were positively related to prevalence and severity of coronary artery disease. In the current research, there was no control group, but white blood cells counts were associated with high osmolality. Only hemoglobin levels were low in the osmolality group. Low hemoglobin levels may be considered as a sign of malnutrition. Elevated levels of osmolality and cardiac risk can be expected in poorly fed cases.

C - reactive protein has also been identified as independent risk marker for mortality also in patients with AMI (20). CRP levels predict the risk for death or AMI within 30 days among patients undergoing percutaneous coronary intervention (21-24). CRP has been suggested to indicate generalized inflammation and participates directly in cardiovascular events (25). The high levels of CK-MB and troponin in the high osmolality group seem to support the idea that osmolality can be a reliable cardiac marker. Osmolality can be useful in risk estimates because it is a non-invasive method that is easy to calculate. Estimating the osmolality of sodium, BUN and glucose in routine tests will provide a cost-effective risk prediction.

Several limitations have to be considered. Data from the present study were collected in a single centre. Patients were the subjects with a cardiovascular problem and the results obtained were not suitable for making a generalization for the community.Patients' biochemical and hemogram measurements were measured only at the time of referral. If we were able to repeat these measurements over a 6-year follow-up, we could reach more useful data. Similarly, in this study, only the mortality of patients was evaluated at 6-year follow-up. If recurrent coronary events were also observed, the relationship between osmolality and coronary artery disease could be discussed in depth.

Conclusion

The higher the osmolality, the worse the six-year survival is in patients with first episode AMI even in the absence of diabetes mellitus and chronic kidney disease. Osmolality is a cheap, noninvasive and reliable parameter to guess long-term survival in patients with coronary heart disease. We

believe that hyperosmolality can be targeted in treatment and prevention efforts as well as its use when evaluating outcomes of the cardiac diseases.

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Declaration of conflict of interest

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