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The association between normal-range admission potassium levels in Israeli patients with acute coronary syndrome and early and late outcomes

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Abstract

Abnormal serum potassium levels are associated with an increased risk of ventricular arrhythmias and mortality in patients with acute myocardial infarction (AMI). The aim of the present study was to evaluate whether different levels of serum potassium, within the normal range, are associated with worse outcomes. The present study comprised 1277 patients with AMI and normal-range admission potassium levels (3.5–5.2 mEq/L), who were enrolled and prospectively followed up in the Acute Coronary Syndrome Israeli Survey between 2010 and 2013. Patients were divided into 4 quartiles based on admission potassium levels; "normal-low" ($K \geq 3.5$ and $K \leq 3.9$), "normal-moderate" ($K > 3.9$ and $K \leq 4.18$), "normal-high" ($K > 4.18$ and $K \leq 4.45$), and "normal-very high" ($K > 4.45$ and $K \leq 5.2$). We analyzed the association between admission serum potassium levels and 7 days in-hospital complication rates, and 30-day and 1-year all-cause mortality rates. Patients with "normal-very high" potassium displayed increased frequency of baseline clinical risk factors and experienced a higher rate of acute kidney injury during hospitalization compared with the "normal-low" group (7.7% vs 2.4%; $P = 0.002$). However, the rate of in-hospital ventricular arrhythmias was similar across the range of admission potassium levels (overall $P = 0.26$), Multivariate analysis showed that compared with "low-normal" potassium values, patients with "normal-very high" potassium levels experienced increased risk for 30-days (adjusted hazard ratio 2.88, 95% confidence interval 1.05–7.87, $P = 0.039$) and 1-year all-cause mortality (adjusted hazard ratio 1.98, 95% confidence interval 1.05–3.75, $P = 0.034$). In patients admitted with AMI, admission serum potassium levels of 4.45 to 5.2 mEq/L are not associated with in-hospital ventricular arrhythmias, but are associated with increased short and long-term mortality.

Abbreviations: ACS = acute coronary syndrome, ACSIS = Acute Coronary Syndrome Israeli Survey, AMI = acute myocardial infarction, CV = cardiovascular, DM = diabetes mellitus, HH = hyporeninemic hypoaldosteronism.

Keywords: acute coronary syndrome, admission serum potassium, ventricular arrhythmia

1. Introduction

Serum potassium levels play a major role in the outcome of cardiovascular (CV) events.[1] Changes in intracellular and extracellular potassium levels modify the electrophysiological properties of the resting membrane potential in cardiac cells and subsequently influence myocardial impulses generation and conduction.[2,3] Serum potassium levels are maintained between 3.5 and 5.2 mEq/L by renal excretion, and shift between intracellular and extracellular fluid compartments.[3] In the early phases of acute myocardial infarction (AMI), the sympathetic nervous system is activated, as reflected by elevated levels of plasma catecholamines[4] and modulation of β adrenergic receptor signaling.[5] This activation leads to intracellular influx of potassium and decrease in serum potassium levels.[6] Low potassium levels have been shown to increase the automaticity and excitability of myocardial cells, leading to the propensity for ventricular arrhythmias.[1]

Several studies have previously illustrated the prognosticator role of profoundly low admission serum potassium, usually below 3.5 mEq/L, and the risk of in-hospital ventricular arrhythmias, among patients with AMI.[4,7–14] In a recent large retrospective study, the authors have found a U-shaped relationship between admission serum potassium levels and in-hospital morbidity and mortality among AMI patients.[15] However, Madias et al[16] did not find admission potassium levels to be a predictor of increased morbidity and mortality among patients with AMI.

Data regarding the association between admission serum potassium levels, within the normal range, and morbidity and mortality outcomes among AMI patients are still lacking. Therefore, in this study we evaluated the association between admission serum potassium levels, within the normal range, and early and late outcomes among AMI patients enrolled in the Acute Coronary Syndrome Israeli Survey (ACSIS).

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2. Methods

2.1. Study design

Acute Coronary Syndrome Israeli Survey is a biannual national ACS survey that prospectively collects data from all patients admitted with ACS during a 2-month period from each of the coronary care units and cardiology wards operating in Israel. A detailed report of the survey design and methods has previously been published.[17] The study protocol was approved by the local institutional review board in accordance with the Declaration of Helsinki, and a waiver of consent has been granted to the investigators.

2.2. Patients

The complete ACSIS 2010 to 2013 survey database includes 1413 subjects. Only subjects with serum potassium levels within the normal values (3.5–5.2 mEq/L) at presentation were included in the current study. Subjects were excluded if their potassium level was lower than 3.5 mEq/L (n = 76) or higher than 5.2 mEq/L (n = 60). Thus, the final study sample comprised 1277 subjects.

2.3. Data collection

Demographic, associated diseases, medical therapy, clinical presentation, admission blood pressure (BP) and heart rate values, electrocardiography, and baseline laboratory results were recorded on prespecified forms for all patients admitted with a diagnosis of ACS.

In-hospital and 30-day outcomes data were ascertained by hospital chart review, telephone contact, and clinical follow-up data. Out-of-hospital 1-year mortality data were ascertained through the use of the Israeli National Population Registry. Data checks for completeness and consistency were based on computerized data queries issued at the coordinating center of the Israeli Association for Cardiovascular Trials and were completed from the medical reports attached to the form of each patient.

2.4. Definitions and end points

Hypertension was defined when a documented diagnosis was reported or when the patient was chronically prescribed antihypertensive medications. Diabetes mellitus (DM) was defined when fasting serum glucose was >126 mg/dL (7.0 mmol/L) on 2 separate readings, a history of DM was reported, or when insulin or oral hypoglycemic were taken. Smoking status was determined according to the questionnaire. Chronic renal failure was defined when a documented medical diagnosis was reported or when the calculated glomerular filtration rate was less than 60 mL/min. Congestive heart failure was defined when a documented medical diagnosis was reported or when the ejection fraction before admission was less than 40%. Dyslipidemia was defined by history, levels of cholesterol on admission and or use of lipids lowering medications.

Patients were divided into 4 quartiles based on admission potassium values: "normal-low" ($K \geq 3.5$ and $K \leq 3.9$ mEq/L) (n = 336), "normal-moderate" ($K > 3.9$ and $K \leq 4.18$ mEq/L) (n = 305), "normal-high" ($K > 4.18$ and $K \leq 4.45$ mEq/L) (n = 321), and "normal-very high" ($K > 4.45$ and $K \leq 5.2$ mEq/L) (n = 315).

End points included 30-day and 1-year all-cause mortality.

2.5. Statistical analysis

For the univariate analysis, percentages were calculated for categorical variables and means with standard deviations for continuous variables. The linear-by-linear association chi-square test in case of categorical variables and the 1-way analysis of variance (ANOVA) test in case of continuous variables.

For the study's 2 outcomes (30-day and 1-year mortality), we depicted Kaplan–Meier survival curves by potassium categories. The curves were statistically compared using the log-rank test for overall.

Cox proportional-hazards models were used for the 30-day and 1-year mortality outcomes. The models were adjusted to prespecified baseline parameters; age, sex, glomerular filtration rate, hypertension, dyslipidemia, and DM.

All *P*-value calculations were 2-tailed and were considered statistically significant if their value was <0.05. The statistical analyses were performed with IBM SPSS version 22.0 (Chicago, IL).

3. Results

The final study population comprised 1277 individuals, mean age was 64 ± 13 years and 991 (78%) were males. Mean follow-up was 482 ± 139 days. Compared with patients with "low-normal" potassium levels, patients with "normal-very high" potassium levels were older and had significantly higher rates of renal failure, DM, and previous myocardial infarctions (Table 1). Patients with "normal-very high" potassium levels had less ST-elevation myocardial infarction and had less reperfusion therapy (Table 1). Preadmission treatment was the same in all groups, and the use of beta-blockers, blockers of the rennin-angiotensin system, and diuretics increased during treatment to the same extent in all groups (Table 2).

3.1. In-hospital complications according to prespecified potassium groups

Subjects in all prespecified groups demonstrated similar rates of most in-hospital complications (Fig. 1). Acute kidney injury was significantly more common among the "normal-very high" potassium group compared with the "normal-low admission" potassium group (7.7% vs 2.4%; $P = 0.002$) (Fig. 1).

3.2. Short and long-term mortality rates

Kaplan–Meier survival analysis showed that cumulative probability of all-cause mortality at 30 days was significantly higher among patients in the "normal-very high" potassium group (6%) as compared with the "normal-low" group (1%), the "normal-moderate" group (3%), and the "normal-high" group (3%) (log-rank *P* value = 0.01 for the overall comparison among the 4 groups during 30-days of follow-up; Fig. 2).

Similarly, when the end point of 1-year mortality was assessed, Kaplan–Meier survival analysis showed that patients in the "normal-very high" potassium group experienced significantly higher 1-year mortality rates (11%) compared with the "normal-low" group (4%), the "normal-moderate" group (5%), and the "normal-high" group (6%) (log-rank *P* value = 0.003 for the overall comparison among the 4 groups during 30-days of follow-up; Fig. 3).

Table 1

Baseline and in-hospital characteristics of patients with acute coronary syndrome by admission systolic blood pressure category

	Low K 3.5–3.9 mEq/L (n = 336)	Normal K 3.91–4.18 mEq/L (n = 305)	High K 4.19–4.45 mEq/L (n = 321)	Very high K 4.46–5.2 mEq/L (n = 315)	P for trend
Age (y)	63 (13.6)	62 (12.7)	64 (12.8)	66 (12.2)	<0.001
Male (%)	245 (73)	249 (82)	254 (80)	243 (77)	0.048
Systolic blood pressure (mm Hg)	142 (30)	142 (27)	141 (28)	140 (27)	0.61
Diastolic blood pressure (mm Hg)	81 (17)	82 (16)	80 (16)	80 (16)	0.38
Heart rate (bpm)	80 (20)	80 (19)	76 (17)	80 (19)	0.026
eGFR (mL/min/1.73 m^2)	76 (27)	79 (25)	72 (28)	66 (26)	<0.001
Body mass index (kg/m^2)	28 (4.8)	28 (4.5)	28 (4.3)	28 (5.5)	0.38
Ejection fraction >50%, n (%)	133 (53)	126 (57)	123 (54)	105 (47)	0.27
Ejection fraction 40%–49%, n (%)	76 (30)	54 (24)	57 (25)	62 (28)	
Ejection fraction 30%–39%, n (%)	32 (13)	32 (14)	36 (16)	39 (17)	
Ejection fraction <30%, n (%)	10 (4)	10 (4.5)	12 (5)	19 (8)	
Killip class I, n (%)	289 (86)	266 (88)	289 (91)	263 (5)	0.178
Killip class II, n (%)	23 (7)	22 (7)	20 (6)	25 (8)	
Killip class III, n (%)	17 (5)	6 (2)	8 (2.5)	14 (4.5)	
Killip class IV, n (%)	5 (1.5)	7 (2)	1 (0.3)	7 (2)	
Troponin elevated (T + I), n (%)	274 (82)	244 (80)	258 (81)	259 (82)	0.92
ST-elevation ECG pattern, n (%)	165 (49)	131 (43)	125 (39)	120 (38)	0.017
Non-ST-elevation ECG pattern, n (%)	170 (51)	173 (57)	194 (61)	195 (62)	
Primary reperfusion therapy, n (%)	136 (41)	98 (32)	96 (30)	89 (28)	0.004
Comorbidities history					
Diabetes mellitus (%)	93 (28)	114 (37)	143 (45)	141 (45)	<0.001
Hypertension (%)	211 (63)	199 (66)	218 (68)	215 (68)	0.4
Dyslipidemia	248 (74)	225 (74)	256 (80)	243 (77)	0.21
Current smoker (%)	121 (36)	113 (38)	120 (38)	110 (35)	0.89
Congestive heart failure (%)	26 (8)	21 (7)	28 (9)	27 (9)	0.82
Cerebrovascular accident (%)	24 (7)	17 (6)	26 (8)	27 (9)	0.5
Chronic renal failure (%)	26 (8)	21 (7)	51 (16)	50 (16)	<0.0001
Previous myocardial infarction (%)	91 (27)	73 (24)	107 (34)	115 (37)	0.002

Values are reported as percentages, means ± SD or median, and interquartile range for eGFR.Combination drug therapy was defined as 2 or more antihypertensive medications.ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; K, potassium.

In the multivariate adjusted regression model, compared with patients with "low-normal" potassium levels, patients with "normal-very high" potassium levels had increased all-cause mortality at both 30 days and 1 year (Table 3) (hazard ratio [HR] 2.88, 95% confidence interval [CI] 1.05–7.87, $P = 0.039$; and HR 1.98, 95% CI 1.05–3.75, $P = 0.034$, respectively).

4. Discussion

We have shown that compared with ACS patients with "low-normal" admission potassium levels, patients with "normal-very high" admission potassium levels had increased all-cause mortality at both 30 days and 1 year. However, we did not find significant differences between groups for in-hospital

Table 2

Medical treatment before admission and post discharge

	Low K 3.5–3.9 mEq/L (n = 336)	Normal K 3.91–4.18 mEq/L (n = 305)	High K 4.19–4.45 mEq/L (n = 321)	Very high K 4.46–5.2 mEq/L (n = 315)	P for trend
Preadmission medical treatment					
Beta-blockers, n (%)	125 (38)	105 (35)	124 (39)	122 (39)	0.65
ACEi/ARB, n (%)	123 (34)	122 (40)	139 (43)	138 (44)	0.21
Calcium antagonists, n (%)	69 (21)	49 (16)	65 (20)	72 (23)	0.21
Diuretics, n (%)*	55 (16)	49 (16)	57 (18)	59 (19)	0.81
K-sparing diuretics, n (%)†	11 (3)	6 (2)	9 (3)	6 (2)	0.62
Postdischarge medical treatment					
Beta-blockers, n (%)	235 (79)	208 (80)	212 (76)	198 (79)	0.77
ACEi/ARB, n (%)	228 (68)	208 (68)	208 (65)	194 (62)	0.26
Calcium antagonists, n (%)	60 (18)	44 (14)	55 (17)	63 (20)	0.32
Diuretics, n (%)*	79 (24)	59 (19)	65 (20)	76 (24)	0.39
K-sparing diuretics, n (%)†	24 (7)	27 (9)	25 (8)	24 (8)	0.88

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

* Diuretics include furosmide and hydrochlorothiazide.

† K-sparing diuretics—all patients received spiranolactone.

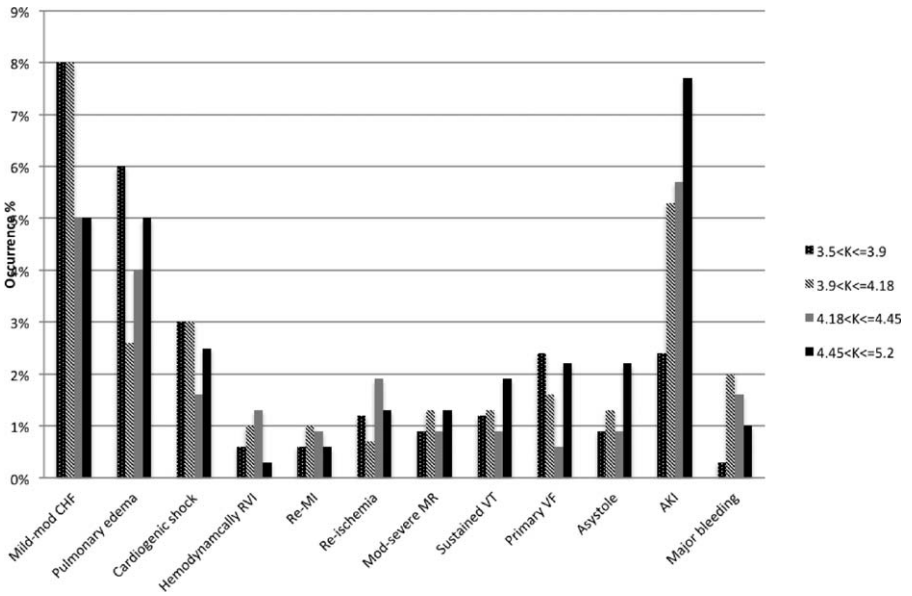

Figure 1. Seven days in-hospital complication rates. Figure shows complication rates (in percentage) at 7 days according to the prespecified potassium groups. AKI, acute kidney injury; CHF, congestive heart failure; MI, myocardial infarction; MR, mitral regurgitation; RVI, right ventricular infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

complication rates, including ventricular arrhythmias. To the best of our knowledge, no studies have previously described the association between normal-range admission potassium levels and mortality outcomes among AMI patients.

Several studies have previously described the relationship of either profoundly low[4,7–14] or extremely high[15] admission potassium levels and increased in-hospital morbidity and mortality, particularly secondary to ventricular arrhythmias. However, most of these studies were relatively small (less than 1000 patients) and were conducted before the era of routine use of beta-blockers and early reperfusion therapies,[4,7–12] which have shown to reduce the incidence of postinfarction mortality and sudden cardiac death.[10,16] Interestingly, Choi et al[18] have recently demonstrated that a U-shaped relation exists between

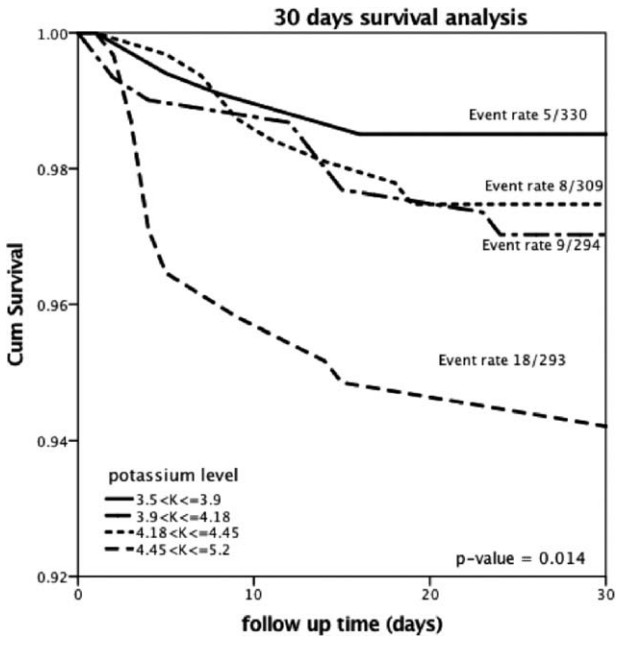

Figure 2. Thirty-day Kaplan–Meier survival analysis. The Kaplan–Meier analysis was used to show mortality probability at 30 days according to the prespecified potassium groups.

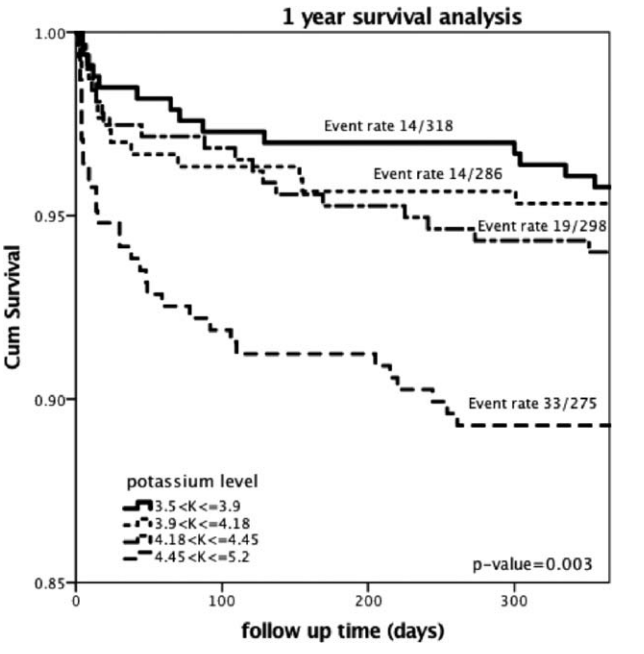

Figure 3. One-year Kaplan–Meier survival analysis. The Kaplan–Meier analysis was used to show mortality probability at 1 year according to the prespecified potassium groups.

Table 3

Multivariate Cox regression analysis

Model	Measure of association	95% Confidence interval		P
30-day mortality	Hazard ratio			
Normal vs low	2.43	0.80	7.36	0.12
High vs low	1.46	0.47	4.52	0.51
Very high vs low	2.88	1.05	7.87	0.039
1-year mortality	Hazard ratio			
Normal vs low	1.27	0.6	2.9	0.54
High vs low	1.25	0.62	2.5	0.52
Very high vs low	1.98	1.05	3.75	0.034

Models adjusted for age, sex, glomerular filtration rate, hypertension, dyslipidemia, and diabetes mellitus.

mean serum potassium levels and 3-year mortality among patients with AMI. In particular, mortality was higher in patients with mean potassium levels above 4.5 mEq/L.[18]

The β_1 adrenergic receptor signaling abnormalities contribute to the development of arrhythmias.[19] During AMI, β_1 adrenergic receptor signaling is associated with cardiac hypertrophy, ventricular remodelling, and subsequently development of ventricular arrhythmias.[19] Inversely, β_2 adrenergic receptor activation has been found to attenuate cardiac remodeling in myocardial ischemic insult, thereby preserving cardiac function after AMI.[20,21] The occurrence rate of the majority of in-hospital complications, including ventricular arrhythmias, was found to be similar across all prespecified groups. This finding is of particular interest compared with previous reports, which emphasized the association of potassium imbalance upon admission and the increased risk for in-hospital ventricular arrhythmias.[4,7–11,13–15] This discrepancy might be explained by the fact that in previous studies, in-hospital morbidity and mortality were only significantly associated with extremely abnormal admission potassium levels, either profoundly low or high, whereas in our analysis, we have only included patients with normal-range potassium levels. Notably, Choi et al have also recently shown that there was no relation between mean serum potassium levels and the occurrence of ventricular arrhythmias.[18]

The prognosticator role of normal range admission potassium levels among patients with AMI have been described in the past. Higher potassium levels (≥4.3 mEq/L) were shown to be an independent risk factor for target lesion revascularization among AMI patients.[22] In addition, higher admission potassium levels (≥4.3 mEq/L) were also found to be associated with a larger scintigraphic infarct size in patients with ST-elevation myocardial infarction.[23] These findings suggest that higher potassium levels, although in the normal range, may be associated with complications that are not necessarily related to immediate changes in the electrophysiological properties of the myocardium, and thus can be associated with late morbidity and mortality. For example, infarct size has been shown to be one of the main determinants of outcome in patients with AMI, even after 6 months.[24] These findings provide a plausible explanation to our results, which demonstrated increased 30-day and 1-year mortality among patients with potassium values of 4.45 to 5.2 mEq/L, yet no increase of in-hospital complication rates, such as ventricular arrhythmias. It is possible that whereas normal range potassium levels are not associated with immediate detrimental conductive aberrancies, they are related to other structural and functional abnormalities which manifest later on, even after several months. Elevated admission potassium levels, even within the normal range, may be an indicator of severe sickness, thereby explaining the increased mortality. We indeed observed a higher rate of DM and renal failure in those with elevated admission potassium levels. Hyperkalemia occurs more frequently in patients with DM compared with nondiabetic patients.[25]. The syndrome of hyporeninemic hypoaldosteronism (HH) is considered the most important causal factor for chronic hyperkalemia in DM patients, but other proposed mechanisms include hyperosmolality, insulin resistance or deficiency, and potassium-sparing antihypertensive medications.[26] Notably, HH has been associated with increased risk of microvascular complications including diabetic nephropathy and neuropathy.[27] Therefore, the increased mortality rates in patients with higher admission potassium levels observed in our study might be confounded by pre-existing DM and renal failure. However, the increase short and long-term mortality in these patients was significant even after adjustment for various comorbidities, including DM and renal function.

Our study has several limitations. It is an observational study and is restricted to Israeli adults, and as such it is unclear whether these findings could be generalized to other populations. We have only data on all-cause mortality and we do not know whether the increased mortality in patients with "normal-very high" admission potassium levels was related to CV causes. In addition, we do not have information regarding the long-term treatment of patients after getting discharged from the hospital, which could affect their survival and hospitalizations. Nevertheless, our analysis included a large number of patients from all intensive cardiac care units and cardiology wards in all public hospitals in Israel. The similar associations of the admission potassium level categories with 2 different end points strengthen the validity of our findings.

In conclusion, our data suggest that admission potassium levels, even when in the normal range, might play a significant role in the risk stratification process of patients presenting with AMI.

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