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RESEARCH ARTICLE

SERUM POTASSIUM LEVEL IS ASSOCIATED WITH CARDIAC ARRHYTHMIAS AND IN-HOSPITAL MORTALITY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Background: Dyskalemia is a risk factor for poor prognosis in patients with acute myocardial infarction (AMI). There is still controversy regarding the optimal level of serum potassium in these patients. **Method:** We studied patients who were admitted with a recorded diagnosis of AMI retrospectively. Using multivariable logistic regression models, we assessed the relationship between admission serum potassium concentration (SPC) and the risk of in-hospital mortality and arrhythmias. Potassium levels were divided as follows: K+< 3.5; K+= 3.5-<4.0; K+= 4.0-<4.5; K+=4.5-5.0; k+> 5.0mmol/l; with K+= 4.0-<4.5mmol/l as reference group. **Results:** Of the 2698 patients included in this study, 38.1% were diagnosed with ST-segment elevation myocardial infarction (STEMI) and 60.3% with non ST-segment elevation myocardial infarction (NSTEMI). Frequency of patients with diabetes, renal failure, atrial fibrillation and 2nd/3rd degree AV block were higher in theK+>5.0mmol/l group and those with Hypertension and ventricular arrhythmia in the K+<3.5mmol/l group. A U-shaped association between admission SPC and in-hospital mortality was observed (OR 1.30; 95% CI: 0.50, 7.35) and (OR 1.21; 95% CI: 0.55, 4.38) in patients with K+>5.0mmol/l and K+<3.5mmol/l respectively. However patients with AMI and diabetes demonstrated a J shaped curve with the highest in-hospital mortality observed in the K+>5.0mmol/l group. The lowest risk for in-hospital mortality was observed in K+=3.5<4.0(OR 0.82; 95% CI: 0.53, 2.19) followed by K+= 4.0-<4.5mmol/l. **Conclusion:** Potassium levels between 4.0 and 4.5mmol/l was relatively safe but not superior to levels between 3.5 and 4.0mmol/l. It might be beneficial to target SPC between 3.5 and 4.0mmol/l.

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INTRODUCTION

Acute myocardial infarction (AMI) is a stressful event that causes intracellular shift of potassium leading to ventricular arrhythmia and sudden cardiac death (Nordrehaug *et al.,* 1985; Kafka, 1987; Sica, 2002). Potassium homeostasis is important for the resting cellular-membrane potential and for transmitting action potential in neuronal, muscular and cardiac tissue, (Gumz, 2015). Adequate distribution of potassium across cell membranes and keeping the extracellular potassium at normal range is maintained by renal excretion and the sodium-potassium ATPase (Na-K-ATPase) pump that drives 2 potassium ions into the cell and 3 sodium ions out of the cell against their concentration gradients (Palmer, 2016).

This Na-K-pump can be stimulated by catecholamine and insulin causing redistribution or movement of potassium into the cell. Based on previous studies, it is recommended to maintain serum potassium concentration in patients with AMI between 4.0 and 5.0mmol/l (Cohn *et al.,* 2000; Zipes, 2006; Antman, 1999) or even higher at a range of 4.5-5.5mmol/l(9). These studies were relatively small observation studies on ventricular arrhythmia occurring after AMI before the b-blocker and reperfusion therapy era. In contrast, several recent studies have demonstrated the association of increase in

mortality in patients with serum potassium greater than 4.5mmol/l. A retrospective cohort study including 38,689 patients with AMI observed a U-shaped relationship between serum potassium and in-hospital mortality with lowest mortality among patients with serum potassium concentration (SPC) between 3.5-4.5mmol/l and higher mortality in SPC higher than 4.5mmol/l or less than 3.5mmol/l.(10). Other recent studies (11-13) had similar findings further confirming the increase in mortality with hyperkalemia and hypokalemia. However, these studies did not fully adjust for AMI subtype (STEMI and NSEMI) or for comorbidities like diabetes, heart failure and renal failure. Also, despite the fact that studies have demonstrated the relationship between hypokalemia and ventricular arrhythmia in patients with AMI, not much is known about the relationship between potassium levels and other arrhythmias like atrial fibrillation and 2nd/ 3rd AV block.

In order to address this discrepancy and get a better understanding of the relationship between admission SPC, cardiac arrhythmias and in-hospital mortality in patients with AMI, we conducted a retrospective study of patients admitted in two hospitals from January 1, 2015 and June 30, 2019. We also aim to bridge the gap in knowledge between admission SPC and other arrhythmias such as atrial fibrillation and 2^{nd}/ 3^{rd} AV block.

MATERIALS AND METHODS

Data sources and study population: This retrospective study was conducted in two teaching hospitals affiliated to Shandong University in the region of Jinan, Shandong province: 1) Qilu Hospital of Shandong University a (4500 beds); 2) Qianfoshan Hospital, Jinan, China (~2300 beds). The study was approved by the ethics community of Shandong University in accordance with the Helsinki declaration.

By reviewing the computerized medical records of every patient admitted with a diagnosis of AMI from January 1, 2015 and June 30, 2019, we collected data on: 1) Demographic characteristics which included patient's age, sex and weight; 2) Clinical characteristics like blood pressure, heart rate; 3) Medical history (hypertension, diabetes, smoking, history of stroke, history of myocardial infarction, etc.); 4) Electrocardiogram findings including corrected QT interval (QTc), STEMI, NSTEMI; 5) Echocardiographic findings like left ventricular ejection fraction (LVEF); 6) Laboratory findings (potassium level, cardiac markers, low density lipoprotein (LDL), liver function tests (LFTs), renal function tests (RFTs); occurrence of arrhythmia during the period of hospitalization and data on mortality (died or survived). In this study we included all patients with a confirmed diagnosis of Acute Myocardial Infarction (AMI) at discharge. We exclude patients with no recorded potassium values.

Outcomes: The primary outcome was in-hospital mortality and the secondary outcomes were ventricular arrhythmia, atrial fibrillation, higher degree atrioventricular block (2^{nd}/3^{rd} degree AV block) and major adverse cardiac events (MACE).

Statistical Analysis: Using IBM SPSS Statistics 25.0 and Stata 15.0 software, baseline characteristics were assessed to compare the patients with AMI categorized by the following admission serum potassium levels: K+< 3.5 (hypokalemia); K+= 3.5-<4.0 (low normal); K+= 4.0-<4.5(normal); K+=4.5-5.0 (high normal); K+> 5.0mmol/L(hyperkalemia). Continuous variables with normal distributions are expressed as mean ± SD and compared using one-way analysis of variance. Categorical variables were expressed as numbers and percentages and Pearson's chi-square test were used to assess the differences. A general linear regression model was created to assess the relationship between serum potassium level and in-hospital mortality, ventricular arrhythmia, atrial fibrillation and 2nd/3rd degree AV block.A multinomial logistic regression was used to assess the odds of adverse clinical outcomes associated to serum admission potassium categories for patients with AMI. The odds ratios indicate the relative risk of ventricular arrhythmia, atrial fibrillation and in-hospital mortality in each potassium level compared with those in the lowest-risk subgroup (4.0-4.5mmol/L).

The following models were generated sequentially to determine the successive influence of potential confounders on the relationship between serum potassium levels. Model (1) age and sex; Model (2) Model 2 adjusted for age, sex and comorbidities (hypertension, diabetes, heart failure, smoking, prior stroke, renal failure, recurrent myocardial infarction, Percutaneous coronary intervention (PCI), Coronary artery bypass graft (CABG); Model (3) including all covariates from model 2 as well as systolic blood pressure, diastolic blood pressure, heart rate, Creatinine kinase-MB (CK-MB), Alanine transaminase (ALT), Aspartate transaminase (AST), Blood urea nitrogen (BUN), LDL-C, Left ventricular ejection fraction (LVEF) and QTc (ms). A two tailed p-value of <0.05 was considered statistically significant.

RESULTS

Patient and baseline characteristics: A total of 2748 records of consecutive patients diagnosed with acute myocardial infarction were identified. Following exclusion of 50 records due to missing data on potassium concentration, 2698 patients with mean age of 64.03±11.86 were included in this study. Of these 1916 (71%) were male and 782 (29%) were female, overall mean admission serum potassium level was 4.14±0.48. Patients were divided into 5 groups and baseline characteristics compared by admission serum potassium level is presented in Table 1. There were 169(6.2%) patients with admission serum potassium K+ <3.5mmol/l, 807(29.9%) patients with K+=3.5-<4.0mmol/l, 1208(44.9%) patients with K+=4.0-<4.5, 431(16%) patient with K+=4.5-5.0mmol/l and 83(3%) patients with K+>5.0mmol/l. 1029 patients (38.1%) had STEMI and 1625(60.3) with NSTEMI. Frequency of patients with diabetes, heart failure and renal failure were higher in the hyperkalemic group and those with Hypertension in the hypokalemic group. The rate of occurrence of in-hospital mortality and atrial fibrillation was highest in the hyperkalemic group(K+>5.0mmol/l) and lowest in the normokalemic group (K+=4.0-<4.5mmol/l) and that of ventricular arrhythmia was highest in the hypokalemic group (K+ <3.5mmol/l) and lowest in the groups (K+=4.0-<4.5 and K+>5.0mmol/l).

The rate of occurrence of 2^{nd} /3^{rd} degree AV block was highest in K+>5.0mmol/l and lowest in K+ <3.5mmol/l. (See Table 1) Admission serum potassium and in-hospital mortality in patients AMI. A total of 202 (7.5%) patients died during the period of hospitalization. After adjustment for age and sex, patients with K+>5.0mmol/l group had the highest mortality (OR of 4.13; 95% CI: 2.01, 10.38).

Table 1. Baseline characteristics of patients with AMI according to admission serum potassium levels

Variables	Admission serum potassium level, mmol/L (2698)					
	K^+<3.5 (n=169)	K^+=3.5-<4.0 (n=807)	K^+=4.0-<4.5 (n=1208)	K^+=4.5-5.0 (n=431)	K^+>5.0 (n=83)	*p* -value
Demographics						
Age	67.2±12.6	63.9±11.3	62.8±11.7	65.2±12.2	70.6±12.2	<0.001
Sex (Male)	93(55.0)	549(68.0)	900(74.5)	319(74.0)	55(66.3)	<0.001
Sex (Female)	76(45.0)	258(32.0)	308(25.5)	112(26.0)	28(33.7)	<0.001
Heart Rate	82.3±17.6	78.4±24.5	75.9±15.0	76.2±15.4	80.1±20.9	<0.001
Systolic blood pressure	131.9±24.5	131.3±37.7	130.3±44.1	127.5±20.8	127.6±25.8	0.485
Diastolic blood pressure	77.1±14.3	76.3±13.0	76.1±21.3	74.2±12.8	71.7±15.2	0.160
History						
Hypertension	122(72.2)	528(65.4)	705(58.4)	244(56.6)	55(66.3)	<0.001
Diabetes	49(29.0)	263(32.6)	385(31.9)	146(33.9)	37(44.6)	<0.001
Smoking	64(37.9)	411(50.1)	664(55.0)	249(57.8)	39(47.0)	<0.003
Recurrent MI	26(15.4)	100(12.4)	174(14.4)	66(15.3)	10(12.0)	<0.001
Angina	94(55.6)	541(67.0)	805(66.6)	275(63.8)	30(36.1)	<0.001
Heart failure	46(27.2)	181(22.4)	232(19.2)	107(24.8)	27(32.5)	<0.001
Stroke	29(17.2)	126(15.6)	178(14.7)	83(19.3)	16(19.3)	<0.001
Renal failure/Dialysis	5(3.0)	16(2.0)	31(2.6)	19(4.4)	13(15.7)	<0.001
Laboratory						
CK-MB (ng/ml)	25.9±57.3	36.8±105.1	30.2±81.7	33.5±84.0	60.4±144.5	<0.001
ALT (U/L)	37.4±72.0	51.1±213.9	47.6±109.6	58.4±132.1	353.3±1010.8	<0.001
AST (U/L)	71.9±79.6	115.0±213.9	89.9±194.4	100.0±213.1	578.2±1795.2	<0.001
LDL-C (mmol/l)	2.6±0.9	2.6±0.9	2.6±0.9	2.6±0.9	2.3±0.8	0.345
BUN (mmol/l)	10.6±46.5	6.4±19.4	6.0±7.9	7.0±5.1	14.1±13.1	<0.001
Creatinine (μmol/L)	96.8±103.4	77.5±45.7	82.2±50.5	93.5±70.6	192.8±186.1	<0.001
LVEF (fraction)	0.5±0.1	0.5±0.1	0.7±6.1	0.5±0.3	0.5±0.1	0.937
QTc (ms)	392.7±61.2	401.3±52.0	397.9±50.3	395.5±52.0	382.8±75.8	<0.001
Hospital course						
STEMI	53(31.4)	324(40.1)	443(36.7)	174(40.4)	35(42.2)	<0.001
NTEMI	114(67.5)	469(58.1)	753(62.3)	252(58.5)	48(57.8)	<0.001
PCI	88(52.1)	512(63.4)	765(63.3)	262(60.8)	38(45.8)	<0.001
CABG	0(0.0)	11(1.4)	33(2.7)	12(2.8)	6(7.2)	0.025
Atrial fibrillation	13(7.7)	54(6.7)	69(5.7)	32(7.4)	12(14.5)	<0.001
Sinus bradycardia	1(0.6)	16(2.0)	14(1.2)	3(0.7)	0(0.0)	<0.001
RBBB/ LBBB	0(0.0)	12(1.5)	20(1.7)	6(1.4)	1(1.2)	<0.001
2nd/ 3rd degree AV block	0(0.0)	2(0.2)	12(1.0)	6(1.4)	3(3.6)	<0.001
Ventricular arrhythmia	12(7.1)	48(5.9)	58(4.8)	25(5.8)	4(4.8)	<0.001
In-hospital mortality	17(10.1)	51(6.3)	69(5.7)	44(10.2)	21(25.3)	<0.001

MI myocardial infarction; CK-MB creatinine kinase-MB; ALT alanine transaminase; AST aspartate transaminase; LDL-C low density lipoprotein-cholesterol; BUN blood urea nitrogen; LVEF left ventricular ejection fraction; QTc corrected QT interval; STEMI ST-segment elevation myocardial infarction; NSTEMI non ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention; CABG coronary artery bypass graft; RBBB/ LBBB right bundle branch block/ left bundle branch block.

Table 2. Odds ratio and 95% confidence interval (CI) for ventricular arrhythmia, atrial fibrillation and in-hospital mortality by admission potassium level in AMI patients

Admission potassium level	No. of patients	No. of events	% of Events	Model 1	Model 2	Model 3
In-hospital mortality				OR(95%CI)	OR(95%CI)	OR(95%CI)
K^+<3.5	169	17	10.1	2.66(1.58, 5.065)	1.57(0.41, 6.60)	1.21(0.55, 4.38)
K^+=3.5<4.0	807	51	6.3	1.83(1.21, 3.52)	1.29(0.35, 5.35)	0.82(0.53, 2.19)
K^+=4.0<4.5	1208	69	5.7	1 (Reference)	1 (Reference)	1 (Reference)
K^+=4.5-5.0	431	44	10.2	2.41(1.61, 4.12)	1.49(0.40, 6.23)	1.02(0.93, 1.25)
K^+>5.0	83	21	25.3	4.13(2.01, 10.38)	1.70(0.31, 14.40)	1.30(0.50, 7.35)
Ventricular arrhythmia						
K^+<3.5	169	12	7.1	2.37(1.35, 5.93)	1.30(0.41, 5.23)	1.12(0.94, 1.12)
K^+=3.5<4.0	807	48	5.9	2.09(1.43, 3.60)	1.16(0.54, 2.75)	0.99(0.95, 1.04)
K^+=4.0<4.5	1208	58	4.8	1 (Reference)	1 (Reference)	1 (Reference)
K^+=4.5-5.0	431	25	5.8	1.90(1.27, 3.63)	1.14(0.47, 3.42)	0.93(0.92, 1.08)
K^+>5.0	83	4	4.8	1.74(0.99, 8.92)	0.92(0.18, 10.64)	0.81(0.80, 1.09)
Atrial fibrillation						
K^+<3.5	169	13	7.7	2.72(1.78, 4.62)	1.75(0.41, 9.30)	1.35(0.88, 2.24)
K^+=3.5<4.0	807	54	6.7	1.18(1.56, 4.27)	1.02(0.54, 3.10)	0.92(0.83, 1.18)
K^+=4.0<4.5	1208	69	5.7	1 (Reference)	1 (Reference)	1 (Reference)
K^+=4.5-5.0	431	32	7.4	1.57(1.10, 3.16)	1.50(0.55, 4.78)	1.03(0.93, 1.24)
K^+>5.0	83	12	14.5	6.25(2.24, 22.42)	3.13(1.12, 11.21)	2.25(1.19, 5.45)
2nd/3rd degree AV block						
K^+<3.5	169	0	0	-	-	-
K^+=3.5<4.0	807	2	0.2	1.84(0.93, 8.24)	1.43(0.81, 5.24)	1.18(0.31, 3.80)
K^+=4.0<4.5	1208	12	1.0	1 (Reference)	1 (Reference)	1 (Reference)
K^+=4.5-5.0	431	6	1.4	2.34(0.75, 7.4)	1.93(0.65, 10.21)	1.35(0.83, 6.18)
K^+>5.0	83	3	3.6	4.14(0.95, 8.52)	3.82(0.62, 15.13)	2.61(0.81, 10.53)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex and comorbidities (hypertension, diabetes, smoking, prior stroke, recurrent myocardial infarction, Percutaneous coronary intervention (PCI), Coronary artery bypass graft (CABG); Model 3: including all covariates from model 2 as well as systolic blood pressure, diastolic blood pressure, Creatinine kinase-MB (CK-MB), Alanine transaminase (ALT), Aspartate transaminase (AST), Low density lipoprotein (LDL-C), Blood urea nitrogen (BUN), Left ventricular ejection fraction (LVEF) and QTc (ms). A two tailed *p*-value of <0.05 was considered statistically significant.

Adjusting for age, sex and comorbidities (Table 2, model 2) followed a slight decrease in the odds ratios. Further adjustment for systolic blood pressure, diastolic blood pressure, heart rate, Creatinine kinase-MB (CK-MB), Alanine transaminase (ALT), Aspartate transaminase (AST), Low density lipoprotein (LDL-C), Blood urea nitrogen (BUN), Left ventricular ejection fraction (LVEF), QTc resulted in further decrease in the odds ratios with patients with K+>5.0mmol and K+<3.5mmol/l having the highest odds of dying in the hospital (OR 1.30; 95% CI: 0.50, 7.35 and OR 1.21; 95% CI: 0.55, 4.38 respectively). Compared to the reference group (4.0-4.5mmol/L), the risk for in-hospital mortality was lower in patients with K+=3.5<4.0 (OR 0.82; 95% CI: 0.53, 2.19). When patients were divided according to AMI subtype, the rate of in-hospital mortality across potassium intervals was higher in NSTEMI compared to STEMI with a U-shaped curve for both subtypes (Figure 1). Patients with AMI and heart failure also demonstrated higher mortality rates with both hyper- and hypokalemia and the rate of event was higher in these patients compared to those without heart failure (Figure 2). However, for patients with diabetes, the highest in-hospital mortality was observed in the K+>5.0mmol/l and the lowest in K+<3.5mmol/l. (Figure 3). Overall MACE (22.5%, *p<0.001*) with the lowest occurrence in K^+=3.5<4.0 group (OR 0.86; 95% CI: 0.13, 2.51). Table 3 Admission serum potassium and ventricular arrhythmia, atrial fibrillation and 2nd/3rd degree AV block in patients AMI.

Ventricular arrhythmia occurred in 147 patients (5.4%), atrial fibrillation in 180 patients (6.7%) and $2^{nd}/3^{rd}$ AV block in 23 patients (0.9%). As shown in Table 2, K+<3.5mmol/l was associated with the highest occurrence of ventricular arrhythmia after adjustment for age and sex with OR 2.37; 95% CI: 1.35, 5.93 and remains the highest with further adjustment in model 2 and 3. After controlling for all confounders, the lowest odd of ventricular arrhythmia occurring is in patients with K+>5.0 (OR 0.81 95%; CI: 0.80, 1.09) and the highest is in K<3.5mmol/l (OR 1.12; 95% CI: 0.94, 1.12). Patients with NSTEMI and those with heart failure showed similar trend (Figure 1 and 2).

In Table 2 model 3 (fully adjusted model), the risk of atrial fibrillation was higher in patients with K+>5.0mmol/l and K+<3.5mmol/l (OR of 2.25; 95% CI: 1.19, 5.45 and 1.35; 95% CI: 0.88, 2.24 respectively). The lowest risk was observed in patients with K+=3.5-4.0mmol/l (OR of 0.92; 95% CI: 0.83, 1.18). Rate of occurrence of $2^{nd}/3^{rd}$ degree AV was lowest in K+<3.5mmol/l regardless of AMI subtype or underlying comorbidity and its incidence increases with increase in potassium levels in patients with STEMI, diabetes and renal failure (see figure 1, 3 and 4).The highest risk was observed in patients with K^+>5.0mmol/l (OR of 2.61; 95% CI:0.81, 10.53) The results of the linear regression analyses are shown in Table 4. Overall the association between potassium levels and each of the four outcomes was not statistically significant. To ensure that the results were not partly driven by specific comorbidity, we performed a linear regression analysis on patients not having heart failure, diabetes and renal failure (Table 5). The results were similar to the main analysis

DISCUSSION

Although the risk of ventricular arrhythmias and mortality in relation to potassium in AMI patients has been the focus of previous studies, there is still controversy around the optimal level of serum potassium in these patients. In this retrospective analysis of 2698 patients with AMI, we assessed the relationship between admission serum potassium levels and the risk of in-hospital mortality and cardiac arrhythmias. We found that outside the normal range of potassium, hypokalemia was observed more frequently than hyperkalemia at admission. Higher mortality rates were observed for K+>5.0mmol/l and K+<3.5mmol/l forming a U-shaped curve for both STEMI and NSTEMI. However, patients with AMI and diabetes demonstrated a J-shaped relationship between admission serum potassium level and mortality with the highest mortality observed in the hyperkalemic group and the lowest mortality in the hypokalemic group. The lowest odd of patients with AMI developing MACE was observed in the group K^+=3.5<4.0mmol/l. Our findings also showed associations of hypokalemia with ventricular arrhythmias even after accounting for confounding factors in multivariable models and hyperkalemia with atrial fibrillation and $2^{nd}/3^{rd}$ degree AV block. Dyskalemia remains one of the most common electrolyte disturbances and it is an important risk factor for adverse events leading to poor prognosis in patients with cardiac diseases and AMI (Goyal, 2012; Xu, 2018; Kjeldsen, 2010).

During AMI, there is an initial surge of catecholamine, which stimulates the sodium–potassium ATPase channel via beta receptors causing an influx of potassium into the cell causing re-distributional hypokalemia. (Brown, 1983) This shift of serum potassium affects resting membrane potentials of the cardiomyocytes, which leads to cellular hyper-polarity with increased excitability and automaticity causing ventricular arrhythmias and sudden cardiac death (Nordrehaug, 1985; Hulting, 1981; Madias, 2000). This phenomenon was demonstrated in our study showing high rates of hypokalemia in patients with AMI at admission. Hyperkalemia on the other hand is observed among patients with additional predisposing conditions like chronic kidney disease and also in patients with underlying comorbidity like diabetes mellitus (Kovesdy, 2016) Potassium homeostasis is maintained by the kidneys, therefore in renal insufficiency, potassium excretion is reduced leading to hyperkalemia. Hyperkalemia is also associated with malignant arrhythmias and all-cause mortality. In our study, the number of patients with renal failure and on dialysis was highest in the hyperkalemic group with an event rate of 15.7%.

Our findings are similar to a recent meta-analysis of cohort studies including seven articles that reported that as compared to AMI patients with potassium levels between 3.5 and <4.0mEq/l, those with either hypokalemia or hyperkalemia were at increased risk of dying (Xi, 2019) A highly powered observational studies by Goyal et al. (2012) suggested the optimal range of serum potassium levels in AMI patients might be at 3.5 and 4.5mEq/l and that potassium levels greater than 4.5mEq/l was associated with increased mortality and should probable be avoided. On the contrary, after a single-centered prospective study of 3714 patients with coronary artery disease (CAD), Peng at al suggested that even though potassium levels of 3.5 to less than 4.5mmol showed the lowest levels of all-cause long term mortality, it was only a predictor of long-term prognosis and not a therapeutic target (Peng, 2015). In the current era, there is widespread use of beta-blockers and early reperfusion therapy in the management of patients with AMI, which has led to a reduction in adverse events in these patients (Timolol-induced reduction in mortality and reinfarction in patients surviving acute

Table 3. Logistics regression analysis for prediction of MACE after AMI

MACE	No. of patients	No. of events	% of events	OR	95%CI
K^+<3.5	169	55	32.5	1.75	0.56, 3.80
K^+=3.5<4.0	807	226	28.0	0.86	0.13, 2.51
K^+=4.0<4.5	1208	352	29.1	1(Reference)	1(Reference)
K^+=4.5-5.0	431	149	34.6	2.10	0.65, 5.24
K^+>5.0	83	26	30.2	1.63	0.22, 3.12

MACE: Major adverse cardiovascular events (recurrent MI + stroke)

Table 4. Result of the linear regression model. The result shows differences in outcomes per 1mmol/l increase/decrease in potassium.

Outcomes	Coefficient	*t*-value	95%CI	*p*-value
In-hospital mortality				
K^+<3.5	0.054	0.877	-0.073, 0.189	0.382
K^+=3.5<4.0	0.100	1.637	-0.020, 0.220	0.102
K^+=4.0<4.5	-0.010	-0.216	-0.101, 0.081	0.829
K^+=4.5-5.0	-0.192	-1.934	-0.386. 0.003	0.054
K^+>5.0	-0.019	-0.231	-0.184, 0145	0.818
Ventricular arrhythmia				
K^+<3.5	-0.003	-0.057	-0.115, 0.109	0.955
K^+=3.5<4.0	0.058	0.967	-0.059,0.174	0.334
K^+=4.0<4.5	0.026	0.609	-0.058, 0.110	0.542
K^+=4.5-5.0	-0.056	-0.735	-0.207, 0.094	0.463
K^+>5.0	-0.007	-0.171	-0.088, 0.074	0.865
Atrial fibrillation				
K^+<3.5	0.010	0.177	-0.106, 0.126	0.860
K^+=3.5<4.0	0.037	0.591	-0.086, 0.161	0.555
K^+=4.0<4.5	-0.079	-1.707	-0.170, 0.012	0.088
K^+=4.5-5.0	-0.094	-1.060	-0.260, 0.078	0.290
K^+>5.0	-0.014	-0.212	-0.147, 0.119	0.832
2nd/3rd degree AV block				
K^+<3.5	-	-	-	-
K^+=3.5<4.0	-0.009	-0.745	-0.034, 0.015	0.457
K^+=4.0<4.5	0.036	1.833	-0.003, 0.075	0.067
K^+=4.5-5.0	-0.066	-1.729	-0.124, 0.009	0.085
K^+>5.0	-0.027	-0.751	-0.097, 0.044	0.455

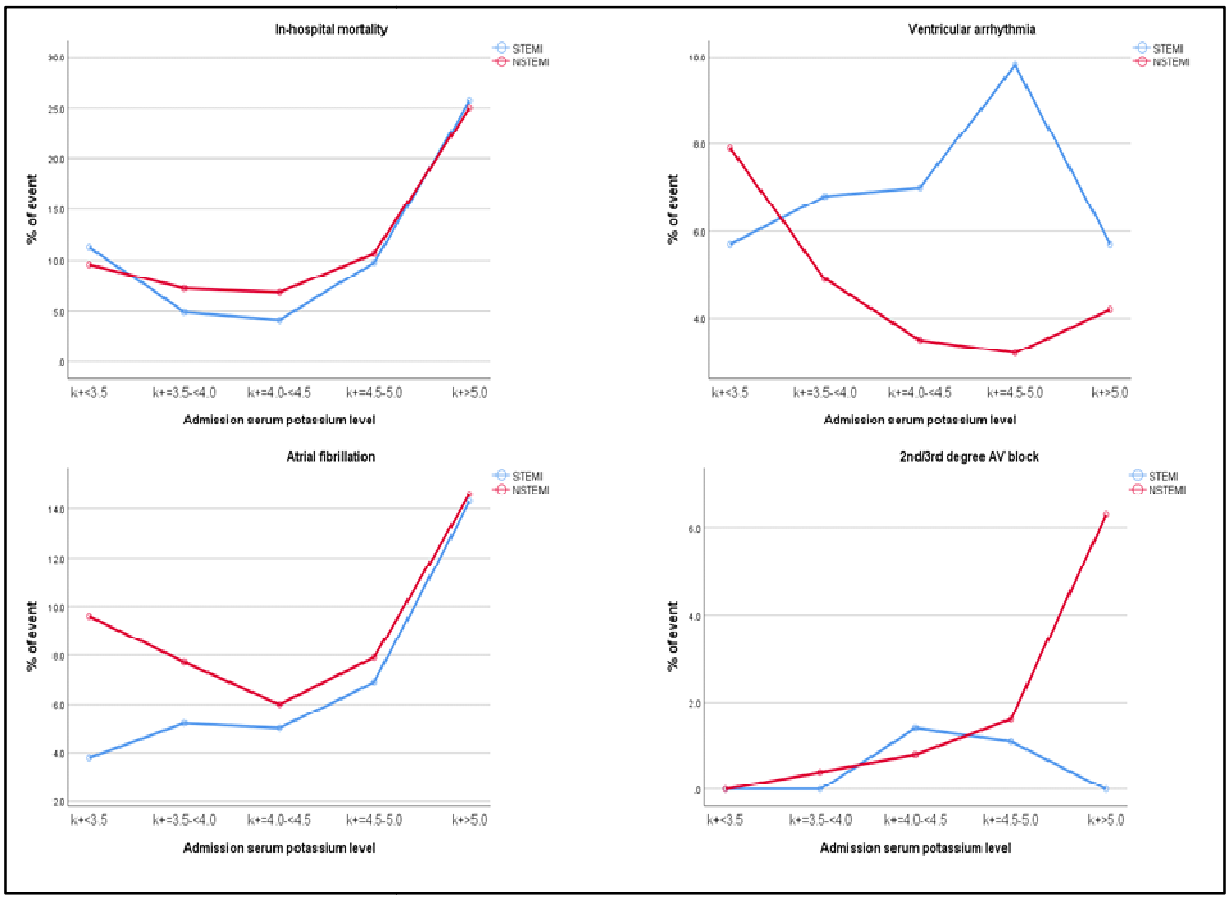

Figure 1. Rate of occurrence of events (in-hospital mortality, ventricular arrhythmia, atrial fibrillation and 2nd/3rd degree AV block) by admission potassium levels in patients with STEMI and NSTEMI

Table 5. Sensitivity analysis: Linear regression model on patients without heart failure, diabetes and renal failure

Outcome	Coefficient	*t*-value	95%CI	*p*-value
In-hospital mortality				
K^+<3.5	-0.064	-0.843	-0.214, 0.086	0.406
K^+=3.5<4.0	0.107	1.309	-0.054, 0.267	0.191
K^+=4.0<4.5	-0.008	-0.137	-0.119, 0.103	0.891
K^+=4.5-5.0	-0.030	-0.210	-0.310, 0.251	0.834
K^+>5.0	0.028	0.084	-0.648, 0.714	0.934
Ventricular arrhythmia				
K^+<3.5	0.053	1.064	-0.460, 0.151	0.290
K^+=3.5<4.0	0.079	1.159	-0.055, 0.212	0.247
K^+=4.0<4.5	0.001	0.029	-0.097, 0.100	0.977
K^+=4.5-5.0	-0.071	-0.743	-0.260, 0.118	0.458
K^+>5.0	-0.201	-1.443	-0.492, 0.089	0.164
Atrial fibrillation				
K^+<3.5	-0.039	-0.645	-0.154, 0.081	0.520
K^+=3.5<4.0	0.055	0.720	-0.095, 0.204	0.472
K^+=4.0<4.5	-0.016	-0.283	-0.129, 0.096	0.777
K^+=4.5-5.0	-0.089	-0.783	-0.315, 0.136	0.435
K^+>5.0	-0.448	-1.604	-1.029, 0.133	0.124
2nd/3rd degree AV block				
K^+<3.5	-	-	-	-
K^+=3.5<4.0	-0.006	-0.359	-0.037, 0.026	0.720
K^+=4.0<4.5	0.018	0.980	-0.018, 0.053	0.327
K^+=4.5-5.0	-0.081	-1.235	-0.216, 0.048	0.218
K^+>5.0	-	-	-	-

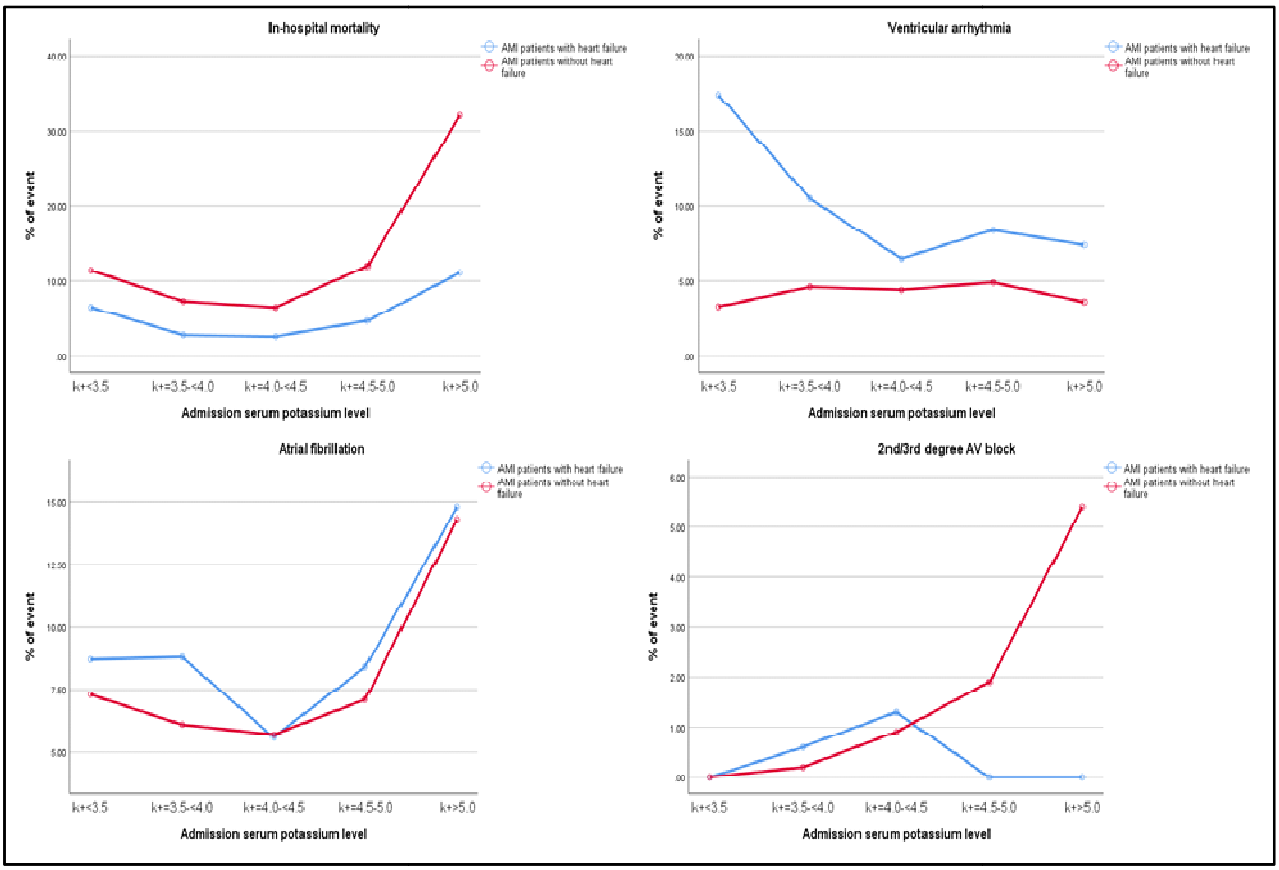

Figure 2: Rate of occurrence of events (in-hospital mortality, ventricular arrhythmia, atrial fibrillation and 2nd/3rd degree AV block) by admission potassium levels in AMI patients with heart failure and AMI patients without heart failure.

myocardial infarction; A randomized trial of propranolol in patients with acute myocardial infarction, 1982). Beta antagonism decreases the occurrence of ventricular arrhythmias by inhibiting the intracellular shift of potassium via sodium potassium pump. In our study, ventricular arrhythmia occurred in 5.4% of the patients. Even though the occurrence of ventricular arrhythmia is still observed in AMI patients, the event rates were far lower compared to earlier studies before the use of beta-blockers. In one prospective cohort study of 2428 patients, Foo et al reported that in acute coronary syndromes, patients with diabetes have significant higher serum potassium concentrations and do not exhibit the early intracellular shift in potassium seen in non-diabetics due to the sympathetic nerve dysfunction that complicates diabetes (Foo, 2003) .A similar trend was demonstrated in our study with diabetic patients being more hyperkalemic. In contrast to report from previous studies (Krijthe, 2013; Olsson, 1981), we found that hyperkalemia was associated with atrial fibrillation. This might be because patients in the hyperkalemic group were older with comorbidities like diabetes, renal failure and

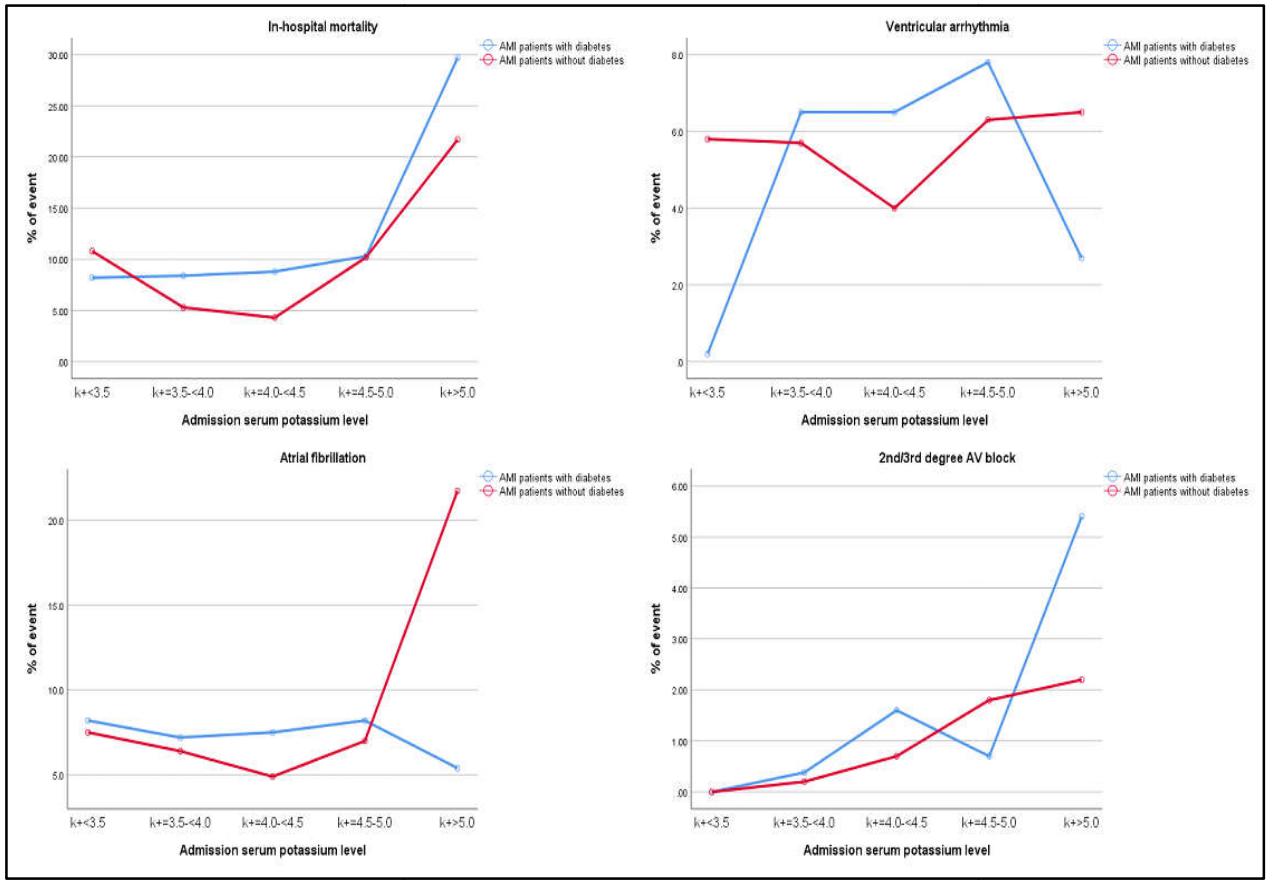

Figure 3: Rate of occurrence of events (in-hospital mortality, ventricular arrhythmia, atrial fibrillation and 2nd/3rd degree AV block) by admission potassium levels in AMI patients with diabetes and AMI patients without diabetes.

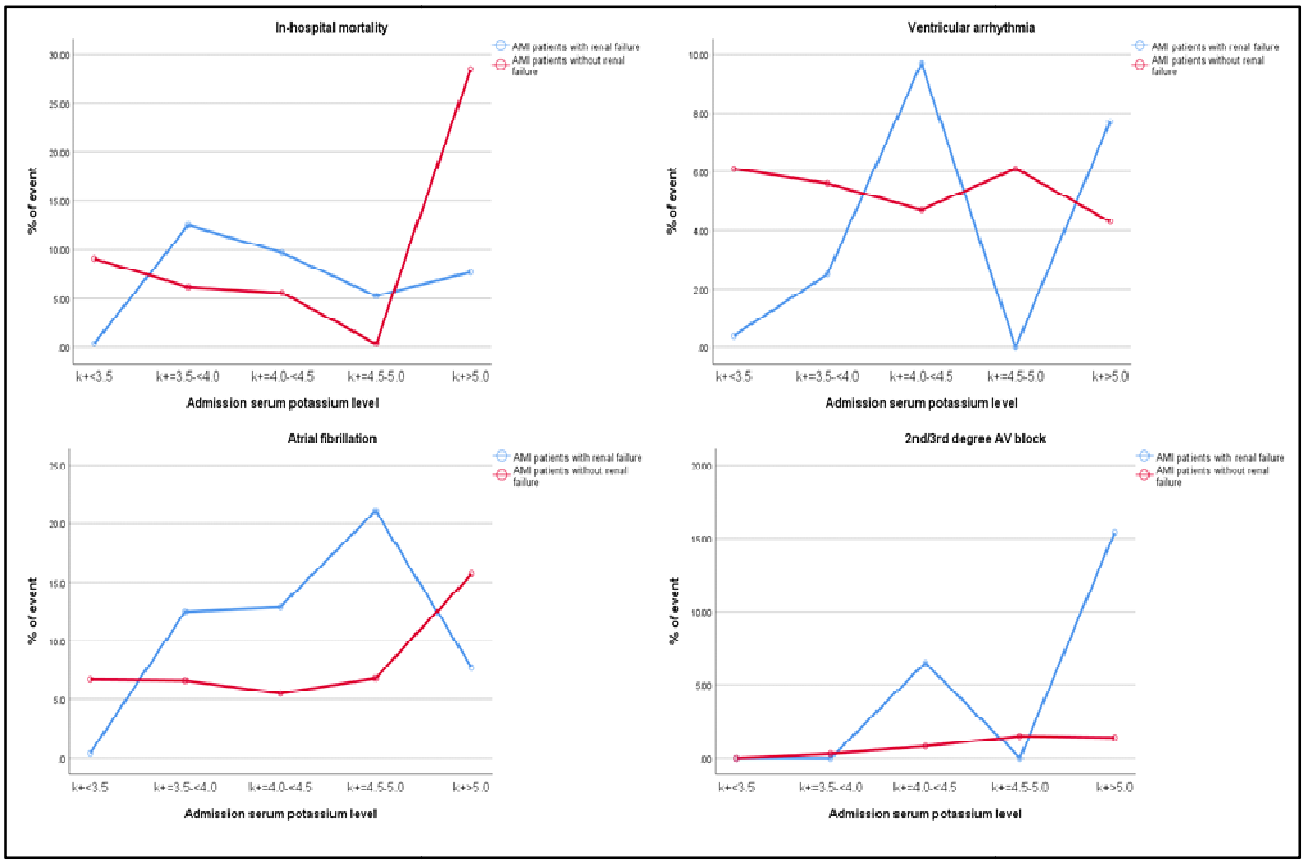

Figure 4. Rate of occurrence of events (in-hospital mortality, ventricular arrhythmia, atrial fibrillation and 2nd/3rd degree AV block) by admission potassium levels in AMI patients with renal failure and AMI patients without renal failure

higher rate of coronary artery bypass surgery (Svagzdiene, 2006). However after full adjustment, we observed that the risk of atrial fibrillation was high in both hyperkalemic and hypokalemic groups. Interestingly, we found a positive correlation between serum potassium level and 2nd / 3rd degree block. This study highlights several interesting associations between admission serum potassium and different types of cardiac arrhythmias in patients with AMI, taking into account the different sub-types (STEMI and NSTEMI) and underlying comorbidity like diabetes mellitus, heart failure and renal failure. Whilst our study has its strengths, there are few limitations to mention. Firstly, this was a retrospective study and due to unavoidable confounders associated with such studies, our findings should be interpreted with caution because association does not mean causation. Addition limitation of our study is that we didn't include the medications patients were on and their effect on serum potassium levels which might have confounded our finding as most cardiac patients are on potassium sparing medications. In Conclusion, both hyperkalemia and hypokalemia at admission in patients with STEMI and NSTEMI are associated with increase in-hospital mortality. It is possible that the U-shaped curve of in-hospital mortality is as a result of the arrhythmic complications seen at both hyper- and hypokalemia. Patients with AMI and diabetes are most likely to be hyperkalemic and mortality in these patients increase with increase in admission serum potassium level, suggesting that hyperkalemia in these patients is more fatal than hypokalemia. Potassium levels between 4.0 and 4.5mmol/l was relatively safe but not superior to levels between 3.5 and 4.0mmol/l. Therefore, it might be beneficial to aim for serum potassium levels between 3.5 and 4.0mmol/l. Furthermore, prospective studies are needed to confirm the appropriate range of serum potassium concentration in patients with AMI and to assess if correction of potassium abnormalities would yield a better outcome.

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REFERENCES

A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982; 247(12):1707-1714.

Antman EM, Anbe DT, Armstrong PW, et al., 2004. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation, 110(5):588-636.

Brown MJ, Brown DC, Murphy MB. 1983. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. *N Engl J Med.,* 309(23):1414-1419.

Choi JS, Kim YA, Kim HY, et al. Relation of serum potassium level to long-term outcomes in patients with acute myocardial infarction. Am J Cardiol 2014; 113(8):1285-1290.

Cohn JN, Kowey PR, Whelton PK, Prisant LM. 2000. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med.,* 160(16):2429-2436.

Foo K, Sekhri N, Deaner A, et al., 2003. Effect of diabetes on serum potassium concentrations in acute coronary syndromes. Heart (British Cardiac Society) 89(1):31-35.

Goyal A, Spertus JA, Gosch K. et al. 2012. Serum potassium levels and mortality in acute myocardial infarction. JAMA. 307(2):157-164.

Gumz ML, Rabinowitz L, Wingo CS. 2015. An Integrated View of Potassium Homeostasis. *N Engl JMed.,* 373(1):60-72.

Hulting J. 1981. In-hospital ventricular fibrillation and its relation to serum potassium. *Acta Med Scand Suppl.,* 647:109-116.

Kafka H, Langevin L, Armstrong PW. 1987. Serum magnesium and potassium in acute myocardial infarction. Influence on ventricular arrhythmias. *Arch Intern Med.,* 147(3):465-469.

Keskin M, Kaya A, Tatlisu MA, et al., 2016. The effect of serum potassium level on in-hospital and long-term mortality in ST elevation myocardial infarction. *Int J cardiol.,* 221:505-510.

Kjeldsen K. 2010. Hypokalemia and sudden cardiac death. *Exp Clin Cardiol.,* 15(4):e96-99.

Kovesdy CP. 2016. Epidemiology of hyperkalemia: an update. *Kidney Int Suppl.,* 6(1):3-6.

Krijthe BP, Heeringa J, Kors JA. et al., 2013. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol.,* 168(6):5411-5415.

Macdonald JE, Struthers. 2004. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol.,* 43(2):155-161.

Madias JE, Shah B, Chintalapally G, Chalavarya G, Madias NE. 2000. Admission serum potassium in patients with acute myocardial infarction: its correlates and value as a determinant of in-hospital outcome. Chest 118(4):904-913.

Nordrehaug JE, Johannessen KA. 1985. Von der Lippe G, Myking OL.Circulating catecholamine and potassium concentrations early in acute myocardial infarction: effect of intervention with timolol. *Am Heart J.,* 110(5):944-948.

Nordrehaug JE, Johannessen KA. 1985. Von der Lippe G.Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. Circulation. 71(4):645-649.

Olsson SB. 1981. Nature of cardiac arrhythmias and electrolyte disturbances. Role of potassium in atrial fibrillation. *Acta Med Scand Suppl.,* 647:33-37.

Palmer BF, Clegg DJ. 2016. Physiology and pathophysiology of potassium homeostasis. Advances in physiology education, 40(4):480-490.

Peng Y, Huang FY, Liu W. et al. 2015. Relation between admission serum potassium levels and long-term mortality in acute coronary syndrome. *Intern Emerg Med.,* 10(8):927-935.

Shiyovich A, Gilutz H, Plakht Y. 2018. Potassium Fluctuations Are Associated With Inhospital Mortality From Acute Myocardial Infarction. Soroka Acute

Myocardial Infarction II (SAMI-II) Project. *Angiology.,* 69(8):709-717.

Sica DA, Struthers AD, Cushman WC, Wood M, Banas JS. 2002. Jr., Epstein M.Importance of potassium in cardiovascular disease. J Clin Hypertens (Greenwich) 4(3):198-206.

Svagzdiene M, Sirvinskas E. 2006. Changes in serum electrolyte levels and their influence on the incidence of atrial fibrillation after coronary artery bypass grafting surgery. *Medicina (Kaunas)*; 42(3):208-214.

Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981; 304(14):801-807.

Xi H, Yu RH, Wang N, Chen XZ, Zhang WC, Hong T. 2019. Serum potassium levels and mortality of patients with acute myocardial infarction: A systematic review and meta-analysis of cohort studies. *Eur J Prev cardiol.,* 26(2):145-156.

Xu H, Faxen J, Szummer K, et al., 2018. Dyskalemias and adverse events associated with discharge potassium in acute myocardial infarction. *Am Heart J.,* 205:53-62.

Zipes DP, Camm AJ, Borggrefe M, et al. 2006. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol.,* 48(5):e247-346.

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