Acta Medica Alanya

RESEARCH ARTICLE

ARAŞTIRMA

Acta Medica Alanya

2022;6(3): 278-284

DOI: 10.30565/medalanya.1172354

Frequency and predictors of hyperkalemia in the heart failure outpatient clinic

Kalp yetmezliği polikliniğinde hiperkaleminin sıklığı ve öngördürücüleri

Gülsüm Meral Yılmaz Öztekin[1*], Ahmet Genç[1], Anıl Şahin[2], Göksel Çağırcı[1], Şakir Arslan[1]

1. Department of Cardiology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey.
2. Department of Cardiology, Sivas Cumhuriyet University, Sivas, Turkey.

ABSTRACT

Aim: Hyperkalemia is a common and potentially life-threatening problem in heart failure (HF). In this study, we aimed to show the frequency of hyperkalemia and related factors in the HF outpatient clinic with real-life data.
Methods: 1 146 patients monitored in the HF outpatient clinic with left ventricular ejection fraction ≤ 40% and potassium level ≥ 3.5 mmol/L were included.
Results: The potassium value of the patients was median 4.6 mmol/L [IQR, 4.3-5]. It was evaluated in three groups as 3.5-5 mmol/L (normokalemia), 5.1-5.5 mmol/L (mild hyperkalemia) and ≥ 5.5 mmol/L (moderate to severe hyperkalemia), according to baseline potassium levels. Mild hyperkalemia was present in 14.5% and moderate to severe hyperkalemia was present in 7.1%. The potassium value was > 5 mmol/L in 21.6% of the patients. The estimated glomerular filtration rate (eGFR) (OR: 0.969, 95% CI: 0.961-0.976, p<0.001), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) (OR: 1.697, 95% CI: 1.124-2.562, p=0.012), and mineralocorticoid receptor antagonists (MRA) (OR: 1.511, 95% CI: 1.066-2.142, p=0.02) were considered as independent factors for hyperkalemia.
Conclusion: eGFR level, ACE-I/ARB, and MRA were associated with hyperkalemia in chronic HF in real-life data.

Key Words: Heart Failure; Hyperkalemia; Potassium; Renin-Angiotensin System.

ÖZ

Amaç: Hiperkalemi, kalp yetmezliğinde (KY) yaygın ve potansiyel olarak yaşamı tehdit eden bir sorundur. Bu çalışmada KY polikliniğinde hiperkalemi sıklığı ve ilişkili faktörlerin gerçek yaşam verileriyle gösterilmesi amaçlanmıştır.
Yöntemler: KY polikliniğinde izlenen sol ventrikül ejeksiyon fraksiyonu ≤ %40 ve potasyum düzeyi ≥ 3.5 mmol/L olan 1146 hasta çalışmaya dahil edildi.
Bulgular: Hastaların medyan potasyum değeri 4.6 mmol/L [IQR, 4.3-5] idi. Başlangıç potasyum düzeylerine göre 3.5-5 mmol/L (normokalemi), 5.1-5.5 mmol/L (hafif hiperkalemi) ve ≥ 5.5 mmol/L (orta-ciddi hiperkalemi) olmak üzere üç grupta değerlendirildi. %14.5'inde hafif hiperkalemi ve %7.1'inde orta ila şiddetli hiperkalemi mevcuttu. Hastaların %21.6'sında potasyum değeri > 5 mmol/L idi. Tahmini glomerüler filtrasyon hızı (eGFR) (OR: 0.969, 95% CI: 0.961-0.976, p<0.001), anjiyotensin dönüştürücü enzim inhibitörü/anjiyotensin reseptör blokeri (ACE-I/ARB) (OR: 1.697, 95% CI: 1.124-2.562, p=0.012) ve mineralokortikoid reseptör antagonistleri (MRA) (OR: 1.511, 95% CI: 1.066-2.142, p=0.02) hiperkalemi için bağımsız faktörler olarak saptandı.
Sonuç: eGFR düzeyi, ACE-I/ARB ve MRA gerçek yaşam verilerinde kronik KY'de hiperkalemi ile ilişkili saptandı.

Anahtar Kelimeler: Hiperkalemi, Kalp yetmezliği, Potasyum, Renin-Anjiyotensin Sistemi.

Received: 07.09.2022 Accepted: 14.11.2022 Published (Online): 31,12,2022

*Corresponding Author: Gülsüm Meral Yılmaz Öztekin, University of Health Sciences, Antalya Training and Research Hospital, Department of Cardiology, Antalya, Turkey, Phone: +90(505)7037670 e-mail: gmeralyilmaz@gmail.com

ORCID: 0000-0001-9540-5075

To cited: Yılmaz Oztekin GM, Genc A, Sahin A, Cagirci G, Arslan S. Frequency and predictors of hyperkalemia in the heart failure outpatient clinic. Acta Med. Alanya 2022;6(3):278-284 doi: 10.30565/medalanya.1172354

INTRODUCTION

Hyperkalemia is a condition characterized by a blood potassium level of > 5.0 mmol/L (mEq/L). This is a critical and problematic situation that is often seen in the clinical follow-up of heart failure (HF) patients [1,2]. The severity of hyperkalemia is defined as mild, with potassium levels >5.0 to <5.5 mmol/L, moderate, between 5.5 and 6.0 mmol/L and severe, > 6.0 mmol/L [1]. Renin-angiotensin-aldosterone system modulators (RAAS-M), known to reduce mortality and recommended by guidelines, are the cornerstone of HF treatment. However, the widespread use of these agents has resulted in an increased incidence of life-threatening hyperkalemia [1,3].

The frequency of hyperkalemia varies according to the reference value. In acute HF, the proportion of potassium levels > 5 mmol/L has been reported to be 35% [4]. In one study, the rate of patients with > 5 mmol/L in the angiotensin-converting enzyme inhibitor (ACE-I) group was reported at 13.5%, and 12.3% in the angiotensin receptor/neprilysin inhibitor (ARNI) group, with the frequency of hyperkalemia at > 5.5 mmol/ L reported as 2.5% vs. 2.2%, respectively [5]. When mineralocorticoid receptor antagonists (MRAs) were added in addition to ACE-I, the incidence of hyperkalemia (> 5.5 mmol/L) has been reported at 11.8% with eplerenone and 13% with spironolactone [6,7].

Many studies have observed the association of potassium levels with mortality in chronic HF [8-10]. Reducing the dose or completely discontinuing RAAS-M due to increased potassium may result in symptoms of withdrawal from this therapy, which has been shown to improve clinical outcomes [11,12].

We aimed to show the frequency of hyperkalemia and related variables, in patients followed up in a specialized HF outpatient clinic.

MATERIALS AND METHODS

1 239 patients with left ventricular ejection fraction (LVEF) ≤ 40%, followed in a tertiary hospital HF clinic between 2015 and 2020, were retrospectively analyzed. 1 156 patients, who were followed up for at least one year and whose potassium level was known at admission, were evaluated for the study. The patients were evaluated according to the basal potassium level at the first HF outpatient clinic admission. Since hyperkalemic and normokalemic patients were to be compared, 10 patients were excluded because their potassium level was < 3.5 mmol/L. Thus, 1 146 patients diagnosed with HF according to the HF Guidelines [2], with LVEF ≤40%, potassium level ≥ 3.5 mmol/L and ≥ 18 years of age, were included in the study. Demographic and biochemical parameters and drugs used by patients were collected from hospital records. In our hospital, potassium levels are measured from serum and other biochemical measurements are standard. The patients were compared in three groups according to their baseline serum potassium levels as 3.5-5 mmol/L, 5.1- < 5.5 mmol/L, and ≥ 5.5 mmol/L [1]. Approval was obtained for the study by the local ethics committee.

Statistical analysis

Statistical analyses were evaluated with the Statistical Package for the Social Sciences software v. 22.0 (IBM Corp.; Armonk, NY, USA). Using the Kolmogorov-Smirnov test, data with normal distribution was presented as standard deviation, and mean and non-normally distributed data was presented as interquartile ranges (IQR) [25-75] as the median. Groups were compared according to normality using the Kruskal-Wallis test or Student's t-test. Categorical variables were provided as numbers and percentages and compared with the Chi-square test. Parameters associated with hyperkalemia were presented as 95% confidence intervals (CI) and odds ratios (OR) by logistic regression analysis. A statistically significant P value was accepted at 0.05.

RESULTS

1 146 eligible HF patients (822 males, 324 females) were included in the study. The median age of the patients was 64 [IQR, 54-73]. 55.8% (n:639) had an ischemic etiology and an LVEF of 30% [IQR, 25-35%]. 53.6% (n:614) had hypertension and 40.1% (n:459) had diabetes. 43% of patients were NYHA II and 24% were NYHA III or IV.

The median potassium value was 4.6 mmol/L [IQR, 4.3-5]. The potassium level of the majority of patients (78.4%) was normal (3.5-5 mmol/L),

while those with mild hyperkalemia (5.1-<5.5 mmol/L) made up 14.5% and moderate to severe hyperkalemia (≥ 5.5 mmol/L) was 7.1%. Only 1% (n:12) of patients had potassium > 6 mmol/L. When the cut-off value of potassium was evaluated as > 5 mmol/L, the frequency of hyperkalemia was 21.6% (n:247). The comparison of variables according to the patient's potassium levels is shown in Table 1. Patients with hyperkalemia were significantly older than patients with normal potassium levels (p<0.001). Most of those with potassium ≥ 5.5 mmol/L were men (p=0.03). In this group, 51.9% of the patients had diabetes (p=0.03) and other comorbidities were similar. Among the laboratory findings, hemoglobin A1c, creatinine, and N-terminal pro-brain natriuretic peptide were higher in the hyperkalemia group (p<0.001, p<0.001, p=0.03, respectively) while estimated glomerular filtration rate (eGFR) and sodium were lower (p<0.001, p<0.001, respectively). The eGFR was < 60 mL/min/1.73m² in 476 (41.5%) of all patients. The rate of GFR < 60 mL/min/1.73m² was higher in patients with moderate to severe hyperkalemia and mild hyperkalemia, than in those with normokalemia (69.1% vs. 54.8% vs 36.6%, p<0.001).

When medical treatments were evaluated, 80.9% (n:927) of the patients were using ACE-I/ARB, 71.1% (n:815) were taking ACE-I and only 9.8% (n:112) were taking ARB. Additionally, only 2.5% (n:29) of patients were using ARNI with, 70% (n:802) using MRA and 92.8% (n:1064) using beta-blockers. While the rate of using any RAAS-M was 89.3% (n:1023), the rate of using MRA together with ACE-I/ARB was 62% (n:710). Of those with hyperkalemia (potassium > 5 mmol/L), 82.2% (n:203) were using ACE-I/ARB, while 64.8% (n:160) were taking both ACE-I/ARB and MRA. The comparison of medical treatments and groups according to potassium levels is given in Table 2. Those who received ACE-I/ARB, MRA and those who take 50% or more of the target dose, were similar between the normokalemia and hyperkalemia groups. In addition, all groups had similar rates of using beta-blockers, ARNI, any RAAS-M and dual RAAS-M (ACE-I/ARB and MRA).

Factors associated with hyperkalemia were examined by logistic regression analysis, which included eGFR, diabetes, hypertension, ACE-I/ARB, MRA and beta-blockers use (Table 3). eGFR (OR: 0.969, 95% CI: 0.961-0.976, p<0.001), ACE-I/ARB (OR: 1.697, 95% CI: 1.124-2.562, p=0.012) and MRA (OR:1.511, %95 CI: 1.066-2.142, p=0.02) were independent variable for hyperkalemia.

DISCUSSION

We analyzed real-life data of patients followed in the HF outpatient clinic. We showed the following: (i) hyperkalemia affected 21.6% of the patients, mild hyperkalemia frequency was at 14.5%, with moderate to severe hyperkalemia frequency at 7.1%; (ii) factors associated with hyperkalemia were eGFR level, ACE-I/ARB and MRA use.

Hyperkalemia is not exceptionally rare in the general population, but its true incidence is unknown; it is estimated to occur in the range of 2 to 3% [13]. The reason for the variation in frequency is that different potassium thresholds are used to define hyperkalemia. In the SOLVD study, hyperkalemia (≥ 5.5 mmol/L) was 6% and severe hyperkalemia (≥ 6.0 mmol/L) was 1.1% during the 2.7-year follow-up [14]. In the PARADIGM-HF study, the ARNI group comprised 16.1% of patients with potassium > 5.5 mmol/L and 4.3% of patients with potassium > 6 mmol/L [15]. In EMPHASIS-HF, the rate of hyperkalemia (>5.5 mmol/L) in patients taking eplerenone was 11.8%, while the rate of severe hyperkalemia (>6 mmol/L) was 2.5% [6]. In the RALES study, in which ACE-I was used in combination with spironolactone, 13% of patients had hyperkalemia (>5.5 mmol/L) and only 2% had severe hyperkalemia (>6 mmol/L) [7]. Similarly, mild hyperkalemia was found at 14.5%, moderate to severe hyperkalemia was found at 7.1% and only 1% of patients had potassium > 6 mmol/L in our study.

Current guidelines support patients with low ejection fraction HF receiving triple therapy, ACE-I/ARB or ARNI, beta-blocker, and MRA. All these drugs are known to be at their greatest effectiveness in recommended target doses tested in clinical trials or tolerated by the patients [2]. RAAS-M used in the treatment of HF are common, with causes of hyperkalemia, and patients with hyperkalemia are more likely to be taking these drugs. However, it has been

Table 1. Baseline characteristics of the patients according to potassium levels.

Variables	K^+ 3.5-5 mmol/L (n =899, 78.4%)	K^+ 5.1-5.5 mmol/L (n=166, 14.5%)	K^+ ≥5.5 mmol/L (n=81, 7.1%)	P-value
Potassium (mmol/L)	4.5 (4.3-4.8)	5.2 (5.1-5.3)	5.7 (5.5-5.9)	<0.001
Age (years)	63 (53-72)	66 (57-73)	68 (60-77)	<0.001
Male, n (%)	647 (72)	109 (65.7)	81.5 (66)	0.03
Female, n (%)	252 (28)	57 (34.3)	15 (18,5)	
BMI (kg/m^2)	26 (24-30)	27 (23-30)	25 (23-28)	0.20
HF duration (months)	12 (3-48)	12 (2-60)	12 (2.5-54)	0.84
LVEF, %	30 (25-35)	30 (24-35)	30 (25-35)	0.29
Causes of HF				
Ischemic, n (%)	495 (55.1)	101 (60.8)	43 (53.1)	0.34
Non Ischemic, n (%)	404 (44.9)	65 (39.2)	38(46.9)	
Medical history				
Diabetes, n (%)	345 (38.4)	72 (43.4)	42 (51.9)	0.03
Hypertension, n (%)	472 (52.5)	93 (56)	49 (60.5)	0.31
Hyperlipidemia, n (%)	346 (38.5)	69 (41.6)	28 (34.6)	0.55
Coronary artery disease, n (%)	461 (51.3)	84 (50.6)	37 (45.7)	0.63
Physical findings				
Systolic BP (mmHg)	110 (100-130)	120 (100-130)	110 (100-130)	0.58
Diastolic BP (mmHg)	60 (60-80)	62 (60-80)	70 (60-80)	0.64
Heart rate (b.p.m)	76 (67-87)	76 (68-86)	75 (65-88)	0.83
Atrial fibrillation, %	170 (18.9)	27 (16.3)	19 (23.5)	0.70
NYHA I, n (%)	297 (33)	52 (31.3)	29 (35.8)	0.66
NYHA II, n (%)	394 (43.8)	68 (41)	31 (38.3)	
NYHA III or IV, n (%)	208 (23.1)	46(27.7)	21 (25.9)	
ICD, n (%)	108 (12)	12 (7.2)	7 (8.6)	0.16
CRT, n (%)	26 (2.9)	4 (2.4)	2 (2.5)	
Laboratory data				
Plasma glucose (mg/dl)	105 (91-139)	109 (91-137)	108 (91-157)	0.87
HbA1c, %	6.3(5,8-7.2)	6.5 (6-7.3)	6.9 (6.1-8.2)	<0.001
Creatinine (mg/dL)	1.08 (0.93-1.3)	1.19 (1-1.48)	1.4 (1.11-1.65)	<0.001
eGFR (mL/min/1.73m^2)	67.5 (52.5-82.5)	56 (42.3-72.7)	50.1 (37.3-66.9)	<0.001
eGFR ≥60, %	570 (63.4)	75 (45.2)	25 (30.9)	<0.001
eGFR <60, %	329 (36.6)	91 (54.8)	56 (69.1)	
Sodium (mmol/L)	139 (137-140)	138 (135-140)	137 (134-139)	<0.001
Albumin (g/dL)	4.2 (3.9-4.5)	4.2 (3.8-4.4)	4.2 (3.7-4.3)	0.11
Calcium (mg/dL)	9.4 (9-9.8)	9.4 (8.9-9.8)	9.5 (9.2-9.9)	0.25
Total cholesterol (mg/dL)	167 (136-204)	167 (129-215)	165 (131-192)	0.74
Haemoglobin (g/dL)	13.2 (11.8-14.5)	12.9 (11.4-14.3)	12.4 (11.2-14.4)	0.05
NT-proBNP (ng/L)	1774 (623-4422)	1930 (720-4238)	2489 (908-8087)	0.03
CRP (mg/dL)	5 (2-11)	5 (2-11)	5.5 (3-11.2)	0.65

K^+, potassium; BMI, body mass index; HF, heart failure; LVEF, left ventricular ejection fraction; BP, blood pressure; b.p.m., beats per minute; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein. eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The p values, between the groups were determined using the Kruskal–Wallis test or the α^2 test. All numerical data are expressed as the median (25-75% interquartile range).

shown that the mortality benefits of these drugs continue, even in hyperkalemia [11,12,16-18]. HF guidelines recommend discontinuing RAAS-M as needed, albeit briefly, and carefully restarting it as soon as possible by monitoring potassium levels [2]. However, because of these concerns, most clinicians choose to cut or reduce dose ACE-I/ARB or MRA when potassium is > 5.5 mmol/L [19]. One of the main reasons for reducing or discontinuing RAAS-M titration is hyperkalemia. Discontinuation

Table 2. Baseline medication of the patients according to potassium levels.

Medication	K^+ 3.5-5 mmol/L (n =899)	K^+ 5.1-5.5 mmol/L (n=166)	K^+ ≥5.5 mmol/L (n=81)	p
ACE-I/ARB, %	724 (80.5)	138 (83.1)	65 (80.2)	0.72
ACE-I, %	643 (71.5)	119 (71.7)	53 (65.4)	0.40
ARB, %	81 (9)	19 (11.4)	12 (14.8)	
ACE-I/ARB, ≥%50 target doses, %	474 (54.4)	96 (58.9)	56 (50)	0.18
MRA, %	624 (69.4)	120 (72.3)	58 (71.6)	0.71
≥%50 target doses,%	470 (61)	89 (63.6)	43 (63.2)	0.31
ARNI, %	23 (2.6)	3 (1.8)	3(3.7)	0.66
Any RAAS-M	802 (89.2)	151(91)	70 (86.4)	0.55
ACE-I/ARB + MRA	550 (61.2)	107 (64.5)	53 (65.4)	0.58
Loop diuretics, %	606 (67.4)	105 (63.3)	56 (69.1)	0.52
Thiazide diuretics, %	208 (23.1)	40 (24.1)	20(24.7)	0.92
Beta-blockers, %	833 (92.7)	157 (94.6)	74(91.4)	0.58
Statin, %	393 (43.8)	66 (39.8)	29 (35.8)	0.27
Acetylsalicylic acid, %	525 (58.4)	96 (58.2)	44 (54.3)	0.77
Digoxin, %	83 (9.2)	11 (6.6)	7 (8.6)	0.55

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists; ARNI, angiotensin receptor/neprilysin inhibitor; RAAS-M, renin-angiotensin-aldosterone system inhibitors. The p values, between the groups were determined using the χ^2 test

Table 3. Logistic regression analysis for hyperkalemia.

Variables	Odds ratio (95% Confidence Interval)	P-value
eGFR	0.969 (0.961-0.976)	<0.001
Diabetes	1.217 (0.896-1.651)	0.208
Hypertension	0.914 (0.671-1.246)	0.571
ACE-I/ARB	1.697 (1.124-2.562)	0.012
MRA	1.511 (1.066-2.142)	0.02
Beta-blockers	1.075 (0.594-1.945)	0.811

eGFR, estimated glomerular filtration rate; ACE-I/ARB, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists.

or dose reduction of these life-saving drugs due to hyperkalemia may play a role in increasing long-term mortality in high-risk HF patients [20-22].

Independent predictors of hyperkalemia were reported as baseline serum creatinine, serum potassium, atrial fibrillation, history of diabetes and NYHA class III or IV [14]. In the CHARM program, male gender, advanced age, baseline hyperkalemia (≥ 5.0 mmol/L), diabetes, creatinine ≥ 2.0 mg/dl and use of ACE-I or spironolactone were defined as risk factors for hyperkalemia [23]. Similarly, in our study, we found eGFR, ACE-I/ARB and MRA to be strong independent predictors for hyperkalemia. Although the diabetes rate and hemoglobin A1c level were higher in those with hyperkalemia, it was not related to diabetes in the regression model. However, we think that it may be indirectly related to low eGFR caused by uncontrolled diabetes.

The use of RAAS-M was common in the PROTECT study, with 75.6% of patients using ACE-I and 45.7% using MRA. Hyperkalemia (potassium > 5 mmol/L) was present in 35% and there was no increase in mortality with hyperkalemia at day 180. However, in this study, reduction and discontinuation of RAAS-M, especially MRAs, were reported as a leading cause of increased mortality [4]. In our study, ACE-I/ARB use was 80.9%, MRA use was 70%, and ACE-I/ARB use together with MRA was 62%. Although the number of patients with potassium > 5 mmol/L was lower (n:247, 21.6%), the rate of MRA use was higher than in the PROTECT study. In addition, in our study, we did not find a significant increase in hyperkalemia in those using ACE-I/ARB, MRA, and those taking at least 50% of the target dose.

Limitations

Our study population was retrospectively obtained

from data belonging to a single center that follows up in the HF outpatient clinic, so the results cannot be generalized to other regions or to our country. However, we think that it can be a catalyst that generates ideas for future studies. We didn't know how long patients took these medications before the potassium assessment, and we did not analyze whether the patients used potassium-binding drugs. Therefore, the effect of potassium binders on outcomes is unknown. Also, medications such as antibiotics, heparins or non-steroidal anti-inflammatory drugs can contribute to hyperkalemia [24]. Since our study was retrospective, information on whether the patients received treatment other than HF treatment at that time is limited. Only the initial potassium values of the patients at the time of their outpatient application and the drugs they were taking were evaluated. Potassium changes or drug changes were not evaluated during follow-up. Another limitation is that in our hospital, serum potassium levels are measured, not plasma. Serum levels can be measured as 0.5 mEq/L higher than plasma levels [1].

CONCLUSION

Hyperkalemia is frequently seen in patients receiving RAAS-M in chronic HF with the recommendation of current guidelines. We found that low eGFR, ACE-I/ARB and MRA were more closely associated with hyperkalemia. Close monitoring and awareness in terms of hyperkalemia in these patients may be important in increasing adherence to treatment.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Funding sources: The authors declare that this study has received no financial support

Ethics Committee Approval: This study was approved by Antalya Training and Research Hospital ethics committee, 08/07/2021, 10/6

ORCID and Author contribution: **G.M.Y.Ö. (0000-0001-9540-5075):** Concept and Design, Data collection, Literature search, Analysis and Interpretation, Manuscript Writing, Critical Review. **A.G. (0000-0003-0797-8418):** Concept and Design, Data collection, Analysis and Interpretation, Critical Review. **A.Ş. (0000-0003-3416-5965):** Concept and Design, Data collection, Analysis and Interpretation, Critical Review. **G.Ç. (0000-0001-9768-918X):** Concept and Design, Analysis and Interpretation, Critical Review, **Ş.A. (0000-0002-2907-4957):** Concept and Design, Analysis and Interpretation, Critical Review.

Peer-review: Externally peer reviewed.

Acknowledgement: No acknowledgement

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