Combined Value Of Contrast Induced Nephropathy and the Cha2ds2-vasc Score for Predicting Mortality In Patients With Acute Coronary Syndrome Who Were Undergoing Percutaneous Coronary Intervention

Eyüp Avcı1, Didar Elif Akgün1, Onursal Buğra2, Ahmet Dolapoğlu2, Aykan Çelik3, Tuncay Kırış3

1 Balıkesir Üniversitesi Tıp Fakültesi, Kardioloji Anabilim Dalı, Balıkesir, Türkiye
2 Balıkesir Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi, Balıkesir, Türkiye
3 İzmir Atatürk Eğitim ve Araştırma Hastanesi, Kardioloji Kliniği, İzmir, Türkiye

ABSTRACT

Introduction: Both contrast induced nephropathy (CIN) and CHA2DS2-VASc score have predictive value for mortality in patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI), whereas the prognostic significance CHA2DS2-VASc of risk score combined with CIN remains unclear. This study was designed to explore the combined value of CIN and CHA2DS2-VASc score for predicting long-term mortality in these patients.

Materials and Method: This retrospective study included 1058 consecutive patients with ACS who were treated with PCI. CIN was defined as a serum creatinine increase ≥ 0.5 mg/dL or ≥ 25% within 48-72 hours after contrast exposure. The patients were divided into two groups as survivors or non-survivors.

Results: The CHA2DS2-VASc score and CIN were independently predictive for all-cause mortality (HR: 1.444, 95%CI: 1.327-1.572, p < 0.001; HR: 1.850, 95% CI: 1.298-2.637, p = 0.001, respectively). Also, Multivessel diseases, Killip ≥2, beta bloker and ACE/ARB use at follow up were independently risk factors for all-cause mortality. Adding CIN on the top of CHA2DS2-VASc score yielded superior risk predictive capacity beyond CHA2DS2-VASc score alone [AUC: 0.735 (0.701- 0.769)], which is shown by improved AUC [AUC: 0.754 (0.720-0.787, difference p = 0.0149)], as well as net reclassification improvement (NRI 28.5%, p < 0.001) and integrated discrimination improvement (IDI 0.021, p < 0.001).

Conclusion: Our study demonstrated that combining the predictive value of CIN and CHA2DS2-VASc score yielded a more accurate predictive value for long-term mortality in ACS patients who underwent PCI as compared to alone CHA2DS2-VASc score.

Keywords: Acute coronary syndrome, mortality, risk score, renal function.

Perkütan Koroner Girişim Uygulanan Akut Koroner Sendromlu Hastalarda Mortalite için Kontrastla İlişkili Nefropati ve Cha2ds2-vasc Skoru Kombinasyonunun Mortalite için Öngördürücü Değeri

Eyüp Avcı1, Didar Elif Akgün1, Onursal Buğra2, Ahmet Dolapoğlu2, Aykan Çelik3, Tuncay Kırış3

1 Balıkesir Üniversitesi Tıp Fakültesi, Kardioloji Anabilim Dalı, Balıkesir, Türkiye
2 Balıkesir Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi, Balıkesir, Türkiye
3 İzmir Atatürk Eğitim ve Araştırma Hastanesi, Kardioloji Kliniği, İzmir, Türkiye

ÖZET

Giriş: Kontrast madde nefropatisinin (KMN) ve CHA2DS2-VASc skorunun, perkütan koroner girişim (PKG) uygulanan akut koroner sendromlu (AKS) hastalarda mortalite için prediktif değeri vardır; oysaki, KMN ile kombine edilmiş olan CHA2DS2-VASc risk skorunun prognostik önemi belirsizliğini korumaktadır. Bu çalışma, bu hastalarda uzun süreli mortaliteyi öngörmek

Hastalar ve Metod: Bu retrospektif çalışmada PKG ile tedavi edilen AKS'li 1058 hasta çalışmaya dahil edildi. KMN, kontrast maruziyetinden 48-72 saat sonra serum kreatinin ≥ 0.5 mg / dL veya ≥% 25 artışı olarak tanımlandı. Hastalar sağ kalanlar ve ölenler olmak üzere iki gruba ayrıldı.

Bulgular: CHA2DS2-VASc skoru ve KMN tüm nedenlere bağlı mortalitenin bağımsız öngördürücüleriydi (HR: 1.444,% 95 CI: 1.327–1.572, p <0.001; HR: 1.850,% 95 CI: 1.298-2.637, p = 0.001, sırasıyla). Ayrıca, çok damar hastalıkları, Killip ≥2, beta bloker ve ACE / ARB kullanımı izlemde tüm nedenlere bağlı mortalite için bağımsız risk faktörleri idi. CHA2DS2-VASc skorunun üstüne CIN eklenmesi, tek başına CHA2DS2-VASc skorunun (AUC: 0.735 (0.701 - 0.769)) ötesinde üstün risk tahmini kapasitesi sağladı, bu da AUC: 0,754 (0.720-0.787, 0.0149)], net yeniden sınıflandırma iyileştirme (NRI% 28.5, p <0.001) ve entegre ayrımcılık iyileştirmesi (IDI 0.021, p <0.001) ile gösterildi.

Sonuç: Çalışmamızda, CIN ve CHA2DS2-VASc skoru combinasyonunun prediktif değerinin, tek başına CHA2DS2-VASc skoruna kıyasla PKG yapılan hastalarda, uzun dönem mortalite için daha doğru bir öngörü değeri sağladığını gösterdik.

Anahtar Kelimeler: Akut koroner sendrom, mortalite, risk skoru, renal fonksiyon.

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Introduction

Acute coronary syndrome (ACS) includes unstable angina (UA), ST-elevation myocardial infarction (STEMI), and non–ST-elevation myocardial infarction (NSTEMI)[1]. These patients are at risk in terms of future cardiac events and thus it is required to make a risk assessment in these patients[2]. Several scoring systems have been used in predicting prognosis and risk assessment in non-ST elevation ACS setting. TIMI (Thrombolysis in myocardial infarction) risk score, PURSUIT (Platelet glycoprotein II/IIIa in unstable angina: receptor suppression using integrilin therapy) risk score, GRACE (Global registry of acute coronary events) risk score are commonly used as risk scores[3-5].

CHA2DS2-VASc scores are used to detect the risk of thromboembolisms and strokes in patients with non-valvular atrial fibrillation[6]. A few studies have evaluated the risk of stroke and mortality by using CHA2DS2-VASc score in ACS patients [7,8]. It has been showed that risk scoring obtained by the addition of creatinine clearance to CHA2DS2-VASc score can predict risk of mortality and stroke[9].

Worsening renal function after administration of contrast media is a well-known complication of invasive cardiovascular procedures. CIN occurs even more frequently after urgent coronary revascularization in patients with STEMI and non-STEMI[10]. Numerous studies have established that the development of contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI) is strongly associated with increased rates of end-stage renal failure, myocardial infarction, repeat revascularization, and early and late mortality[11].

In the present study, we aimed to investigate whether the addition of CIN to CHA2DS2-VASc score creates additional prognostic value for all-cause mortality in patients with ACS treated with PCI.

Materials and methods

Study population

We enrolled 1058 consecutive ACS patients with normal sinus rhythm treated with PCI from april 2008 and February 2015. Diagnosis of STEMI, NSTEMI and UA were established in accordance with published guidelines[1,12]. Exclusion criteria were severe valvular heart disease, end-stage chronic obstructive pulmonary disease and end-stage malignant disease. Other exclusion criteria were young (<20 years) and elderly (>90 years) patients, patients with normal coronary arteries or less than 50%

stenosis in a major vessel, and those with a life expectancy of less than one year. We recorded medical treatment and admission laboratory values on admission of all patients. The retrospective study was approved by the Ethics Committee of Balikesir University.

Calculation of CHA2DS2-VASc and CIN

We used combined CHA2DS2-VASc score and CIN for predicting total mortality after ACS underwent PCI. Stroke, dyslipidemia, diabetes mellitus (DM), and hypertension (HT) were defined according to current guidelines[13]. Current smokers were defined as having a history of smoking for a certain period within the past year. The CHA2DS2–VASc score was calculated for each patient by assigning 1 point each for the presence of heart failure (HF)/left ventricular ejection fraction <40%, hypertension, diabetes, vascular disease, 65–74 years of age or female sex, and 2 points for a history of stroke or age ≥75 years[14].

CIN was defined as a serum creatinine (sCr) increase ≥ 0.5 mg/dL or≥25% within 48-72 hours after contrast exposure [10].

Statistical analysis

Continuous variables are presented as means ± SD, whereas dichotomous variables are described as numbers and percentages. The differences among the two groups were compared using the chi-square test for categorical variables and Student's *t* tests or Mann Whitney U test for continuous variables. A multivariate Cox regression analysis was performed to identify independent predictors for the primary end point. Factors entered into the multivariate model comprised those with p-values < 0.1 from the univariate analysis and variables with known prognostic value. The predictive values of CHA2DS2-VASc score and a combination of CIN and CHA2DS2-VASc score were estimated by comparing the areas under the receivers operating characteristic (ROC) curve. Comparison of receiver operating characteristics (ROC) curves, which was caried out by DeLong's test[22] was performed with NCSS 12 software programme. Also, the increased discriminative value after the addition of CIN to CHA2DS2-VASc score was also estimated using the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI)[25]. Statistical analysis was performed using the Statistical Package for Social Sciences, version 16 (SPSS Inc., Chicago, IL, USA). A p-value<0.05 was considered to indicate statistical significance.

Results

Total 1058 patients (survivors = 796 and non-survivors= 262) were included in this study. The median follow-up period was 69.7 months (inter-quartile range 25th and 75th percentile: 42.8 to 80.8 months). Baseline characteristics of the study groups were presented in Table 1. The mean age of survivors patients was 59 ± 11 years and 24% (187) of the patients were female. Non-survivors were older (68 ± 12 vs 59 ± 11 years, p < 0.001) and had a higher prevalence of diabetes mellitus (DM) (36% vs 22%, p < 0.001). Compared with survivors, history of heart failure, hypertension (HT), previous coronary artery disease (CAD), and higher Killip class were more frequent in non-survivors. On the other hand, use of beta-blockers and angiotensin-converting enzyme inhibitors were lower in non-survivors than survivors (Table 1).

The rate of CIN in non-survivors was higher than survivors (19% vs 4% p < 0.001). Compared with survivors, CHA2DS2-VASc score was higher in non-survivors [2(1-3) vs 4(3-5), p < 0.001].

The laboratory variables of the groups are shown in Table 2. LVEF was significantly lower in non-survivors than survivors (44.7 ± 10.6% vs 49.5 ± 9.4% p < 0.001). Non-survivors had higher levels of sCr than survivors. Moreover, Hemoglobin level were higher in non-survivors compared with survivors. In contrast, glomerular filtration rate (GFR) were lower in non-survivors than survivors

The independent predictors for all-cause mortality identified using the multivariate Cox regression analysis are presented in Table 3. CHA2DS2-VASc score and CIN were independently predictive for all-cause mortality (HR: 1.444, 95%CI: 1.327–1.572, p < 0.001; HR: 1.850, 95% CI: 1.298-2.637, p =0.001, respectively, Table 3). Also, Multivessel diseases, Killip ≥2, beta bloker and ACE/ARB use at follow up were independently risk factors for all-cause mortality in multivariate cox regression analysis.

AUC of CHA2DS2-VASc score for all-cause mortality was 0.735 (0.701-0.769, p <0.001 Figure 1). Compared with the CHA2DS2-VASc score alone, the combining CIN with CHA2DS2-VASc score was associated significant improvement in the ability to predict mortality (AUC:0.735 vs 0.754, p = 0.0149, Fig. 1). In addition, compared to baseline CHA2DS2-VASc scoring system, the expanded risk model with CIN plus CHA2DS2-VASc score resulted in superior discrimination for mortality with an NRI of 28.5% (p < 0.001) and IDI of 0.021 (p < 0.001).

Discussion

This study demonstrated that CHA2DS2-VASc score and CIN were associated with increased all-cause mortality in ACS patients treated with PCI. To the best of our knowledge, this is the first study investigating the combining of CIN with CHA2DS2-VASc score for predicting mortality in these patients. Morever, the present study showed that the combined use of CIN and CHA2DS2-VASc score was better able to predict all-cause mortality compared with the CHA2DS2-VASc score alone.

In previous studies, CHA2DS2-VASc score to prevent thromboembolic events was used to determine the need for anticoagulant therapy in patients with atrial fibrillation, but it was not used as a predictor of mortality[15,16]. Each of CHA2DS2-VASc's components has a prognostic importance for CAD. Advanced age is a significant risk factor for mortality[17]. Similarly, HT, DM, and heart failure has been shown to be a long term prognostic indicator[18,19]. Malmberg et al. have reported that DM was an independent predictor for all-cause mortality, as well as cardiovascular death, recurrent myocardial infarction, stroke, and congestive heart failure in unstable angina or non-Q-wave myocardial infarction patients[20]. In our study, patients with high CHA2DS2-VASc score had a higher rate of HT, DM, and heart failure and they were also older. Compared with men, women have more in-hospital complications and mortality rates in patients with ACS[21,23]. The proportion of women was higher in patients with high CHA2DS2-VASc score and CIN. Therefore, this may have contributed to the high mortality in these patients.

Kim and colleagues have shown that CHA2DS2-VASc score can be used in determining prognosis in acute myocardial infarction patients regardless of presence of atrial fibrillation[24]. In this study, patients were divided into four groups according to the CHA2DS2-VASc score. Patients with high score were older and female. Although in-hospital mortality was not different among four groups (p=0.75), it has been shown that the cardiac events were increased with the elevated score points. In subgroup analysis, the CHA2DS2-VASc score has been shown to be of predictive value in predicting mortality in patients with NSTEMI as found in our study. Furthermore, when we added the CIN to this score, combining CIN to CHA2DS2-VASc score was better able to predict all-cause mortality compared with the CHA2DS2-VASc score alone.

Serum creatinine levels has a significant prognostic value in ACS patients. It has been shown that baseline renal dysfunction was associated with a higher mortality in patients with ACS as found in our study[26]. Similarly, renal dysfunction has been shown to be independently associated with mortality STEMI patients treated with primary PCI[26]. Deterioration of renal function can occur due to many reasons during the ACS setting. Its most common cause is contrast nephropathy[27,28]. In our study, contrast volume was similar among the two groups. In addition, there was no significant difference in deterioration of renal function between the patients who underwent PCI and who did not. Nobuhiro et al. have reported that the in-hospital deteriorating renal function is an independent indicator for mortality in patients with ACS who underwent PCI[29]. Similarly, another study has shown that the deterioration of renal function during hospitalization was associated with long term mortality in patients admitted to the hospital with the diagnosis of ACS[30].

Several factors associated with impaired renal function such as insulin resistance, oxidative stress, inflammation, endothelial dysfunction, reninangiotensin- aldosterone system activation, and increased plasma levels of fibrinogen and homocysteine may contribute to the adverse outcome of patients with acute coronary syndrome[31-33]. Furthermore, patients with renal dysfunction have a higher prevalence of baseline cardiovascular comorbidities such as diabetes, heart failure, previous MI and stroke and coronary interventions as our study[34]. In addition, diffuse coronary artery disease proven by angiography was more frequent in these patients as our study. All these conditions may related to adverse prognosis in patienst with ACS[35].

Consequently, our findings might be correlated with well-known predictors such as DM, HT, advanced age, heart failure, female gender, renal dysfunction with respect to cardiovascular mortality for ACS patients. Thus, these findings may explain why the adding CIN to CHA2DS2-VASc score and will be used to predict mortality for ACS patients undergoing PCI.

Our study has some limitations. The database analysis is retrospective in nature. Therefore, it is necessary to perform a prospective cohort study to evaluate the prognostic role of the combining CHA2DS2-VASc with CIN more accurately. Moreover, some confounders of CIN, such as proteinuria and nephrotoxic agents, could not be fully assessed.

Conclusion

The CHA2DS2-VASc score is a simple score derived from an easily-accessible and non-invasive blood test. Similarly, CIN may be easily determined by a serum creatinine levels. They were independently associated with all-cause mortality in ACS patients undergoing PCI. Furthermore, adding CIN to CHA2DS2-VASc score improved the predictive value for all-cause mortality in these patients.

Conflicts of interest

There are no conflicts of interest.

Authorship contributions

Concept/Design: EA,DEA

Analysis/Interpretation:OB,AD,AÇ

Data Acquisition: EA,DEA

Writting: TK,EA,AD

Critical Revision: TK.EA

Final Approval: All of authors

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Table 1. Baseline characteristics of the study population.

Variable	Survivors (n = 796)	Non-survivors (n = 262)	P-value
Age (year)	59 ± 11	68 ± 12	< 0.001
Female n (%)	187 (24)	97 (37)	< 0.001
HF or LVEF < 40% n (%)	107 (13)	82 (31)	< 0.001
Hypertension n (%)	367 (46)	165 (63)	< 0.001
Diabetes mellitus n (%)	176 (22)	95 (36)	< 0.001
Hyperlipidemia n (%)	187 (24)	51 (20)	0.176
Current smoking n (%)	346 (43)	83 (32)	0.001
Previous CAD n (%)	175 (22)	92 (35)	< 0.001
Prior stroke/TIA n (%)	19 (2)	22 (8)	< 0.001
Type of ACS n (%)			0.489
STEMI	476 (60)	144 (55)	
NSTEMI	227 (29)	86 (33)	
UA	93 (12)	32 (12)	
Killip class ≥ 2 n (%)	34 (4)	44 (17)	< 0.001
Multivessel disease n (%)	248 (32)	118 (45)	< 0.001
CHA2DS2-VASC score	2 (1-3)	4 (3-5)	< 0.001
Medication at discharge			
Beta-blocker n (%)	684 (86)	200 (76)	< 0.001
Statin n (%)	667 (85)	208 (80)	0.044
ACE-I/ARB n (%)	685 (87)	194 (75)	< 0.001
Outcomes			
In-hospital death n (%)	0 (0)	20 (8)	< 0.001
Stroke n (%)	15 (2)	12 (5)	0.016
HF admission n (%)	18 (2)	27 (10)	< 0.001
Myocardial reinfarction n (%)	82 (10)	22 (8)	0.369

TVR n (%)	100 (13)	23 (9)	0.097
CIN n (%)	32 (4)	49 (19)	< 0.001

HF: heart failure, CAD; coronary artery disease, TIA: transient ischemic attack, ACE-I: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blocker, ACS: acute coronary syndrome, UA: unstable angina, NSTEMI: non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, TVR; target vessel revascularization, CIN: contrast induced nephropathy, CHA2DS2-VASC; heart failure /left ventricular ejection fraction <40%, hypertension, history of stroke , age ≥75 years diabetes, vascular disease, age 65–74 years, female sex.

Table 2. Laboratory results of the study groups.

Variable	Survivors (n = 796)	Non-survivors (n = 262)	P value
SCr* $_{adm}$ (mg/dl)	0.85 (0.76-1.02)	0.96 (0.80-1.30)	< 0.001
Hemoglobin (g/dl)	14.0 ± 1.8	13.0 ± 2.2	< 0.001
LVEF (%)	49.5 ± 9.4	44.7 ± 10.6	< 0.001
GFR (mL/minute/1.73 m^2)	85.6 ± 21.6	69.2 ± 25.7	< 0.001

SCr; serum creatinine at admission, LVEF; left ventricular ejection fraction, GFR; glomerular filtration rate.

* Comparison was made using Mann-Whitney *U* test at *P* <0.05, and these values were described by median with inter-quartile range (25^{th} and 75^{th} percentile).

Table 3. Independent predictors of all-cause mortality.

Variable	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age * (per 1 year)	1.063	1.052-1.075	<0.001	1.023	1.008-1.038	
Female*	1.746		<0.001	0.944	0.666-1.354	
Diabetes mellitus*	1.868	1.359-2.244	<0.001	1.384	1.004-1.907	
Hipertension*	1.708		<0.001	0.999	0.719-1.390	
Stroke history*	3.097	1.451-4.799	<0.001	1.954	1.193-3.200	
History of CAD*	1.780		< 0.011	1.113	0.804-1.542	0.015
HF or LVEF < 40*	2.525	1.329-2.196	<0.001	0.812	0.395-1.669	<0.001
Multi-vessel disease	1.918		<0.001	1.393	1.067-1.818	
Killip class ≥ 2	3.946	1.799-3.280	<0.001	3.202	2.256-4.544	
LVEF *(per 1% change)	0.957	1.944- 3.280	<0.001	0.972	0.958-0.986	0.011
Hemoglobin (per 1 mg/dl)	0.803	1.380-2.294	<0.001	0.887	0.816-0.965	0.005
Creatinine Þ (mg/dl)	0.977	1.500-2.451	<0.001	0.676	0.760-0.848	<0.001
GFR Þ (mL/minute/1.73 m^2)	0.594	2.852-5.460	<0.001	0.646	0.946-0.969	
B-blocker use at follow-up	0.688		<0.001	1.116	1.024-1.103	
ACE-I/ARB use at follow-up	1.537	1.164-1.405	<0.001	1.444	1.164-1.405	
Statin use at follow-up	4.038	0.972-0.981	<0.001	1.850	0.444-0.917	<0.001
CHA2DS2-VASC score		0.446-0.790	<0.001		0.500-0.915	0.001
CIN		0.359-0.631			0.475-0.878	

		0.507-0.933		1.327-1.572
		1.435-1.645		1.298-2.637
		2.956-5.517		

HR: hazard ratio, CI: confidence interval, LVEF: left ventricular ejection fraction, CAD: coronary artery disease, GFR: glomerular filtration rate, CHA2DS2-VASC: heart failure /left ventricular ejection fraction <40%, hypertension, history of stroke , age ≥75 years diabetes, vascular disease, age 65–74 years, female sex , CIN: contrast induced nephropathy, ACE-I/ARB: angiotensin-converting enzyme inhibitors/ angiotensin-reseptor blocker, HF: heart failure.

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Figure 1.ROC analysis of CHA2DS2-VASc and CHA2DS2-VASc plus CIN