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

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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.

Patients and Methods: 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 nonsurvivors.

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 blockers, and ACE/ARB use at follow-up were independently risk factors for all-cause mortality. Adding CIN on top of the 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 the CHA2DS2-VASc score yielded a more accurate predictive value for long-term mortality in ACS patients who underwent PCI as compared to the CHA2DS2-VASc score alone.

Key Words: Acute coronary syndrome; mortality; risk score; renal function

Perkütan Koroner Girişim Uygulanan Akut Koroner Sendromlu Hastalarda Kontrastla İlişkili Nefropati ve CHA2DS2-VASC Skoru Kombinasyonunun Mortalite için Öngördürücü Değeri

ÖZET

Giriş: Kontrast madde nefropatisi (KMN)'nin 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 için KMN ve CHA2DS2-VASc skorunun kombine değerini araştırmak üzere tasarlanmıştır.

Hastalar ve Yöntem: 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 anjiyotensin dönüştürücü enzim/anjiyotensin reseptör blokerleri (ACE/ARB) kullanımı izlemde tüm nedenlere bağlı mortalite için bağımsız risk faktörleri idi. CHA2DS2-VASc skorunun üstüne KMN 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.

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Sonuç: Çalışmamızda, KMN ve CHA2DS2-VASc skoru kombinasyonunun 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

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 conduct a risk assessment in these patients[2]. Several scoring systems have been used in predicting prognosis and risk assessment in non-ST-elevation ACS settings. Thrombolysis in myocardial infarction risk score, PURSUIT (Platelet glycoprotein II/IIIa in UA: receptor suppression using integrilin therapy) risk score, and 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 nonvalvular atrial fibrillation[6]. A few studies have evaluated the risk of stroke and mortality by using the CHA2DS2-VASc score in ACS patients[7,8]. It has been shown 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 the CHA2DS2-VASc score creates additional prognostic value for all-cause mortality in patients with ACS treated with PCI.

PATIENTS and METHODS

Study Population

We enrolled 1.058 consecutive ACS patients with normal sinus rhythm treated with PCI from April 2008 and February 2015. Diagnoses 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 upon admission of all patients. Although this study was designed as retrospective, the patients were followed prospectively. The retrospective study was approved by the Ethics Committee of Balikesir University (No:139/2018).

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, being 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]. Iohexol as contrast media was used in all patients.

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 receiver operating characteristic (ROC) curve. Comparison of ROC curves, which was carried out by DeLong's test, was performed with NCSS 12 software program[15]. Also, the increased discriminative value after the addition of CIN to the CHA2DS2-VASc score was also estimated using the NRI and Integrated Discrimination Improvement (IDI)[16]. 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

A total of 1.058 patients (survivors= 796 and nonsurvivors= 262) were included in this study. The median follow-up period was 69.7 months (interquartile 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 was 59 ± 11 years, and 24% (187) of the patients were female. Nonsurvivors were older (68 ± 12 vs. 59 ± 11 years, p< 0.001) and had a higher prevalence of 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 nonsurvivors. On the other hand, use of beta blockers and angiotensin-converting enzyme inhibitors were lower in nonsurvivors than survivors (Table 1).

The rate of CIN in nonsurvivors was higher than survivors (19% vs. 4% p< 0.001). Compared with survivors, CHA2DS2-VASc score was higher in nonsurvivors [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 nonsurvivors than survivors (44.7 ± 10.6% vs. 49.5 ± 9.4% p< 0.001). Nonsurvivors had higher levels of sCr than survivors. Moreover, Hemoglobin level were higher in nonsurvivors compared with survivors. In contrast, glomerular filtration rate (GFR) were lower in nonsurvivors 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 of 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 blockers, 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, combining CIN with the CHA2DS2-VASc score was associated with significant improvement in the ability to predict mortality (AUC: 0.735 vs 0.754, p= 0.0149, Figure 1). In addition, compared to the 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. Moreover, the present study showed that the combined use of CIN and the CHA2DS2-VASc score was better able to predict all-cause mortality compared with the CHA2DS2-VASc score alone.

Table 1. Baseline characteristics of the study population

Variable	Survivors (n= 796)	Nonsurvivors (n= 262)	p
Age (years)	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, LVEF: Left ventricle ejection fraction, 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)	Nonsurvivors (n= 262)	p
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_{adm}: Serum creatinine at admission, LVEF: Left ventricular ejection fraction, GFR: Glomerular filtration rate.

* Comparisons were made using the Mann-Whitney U test at p< 0.05, and these values were described by median with interquartile range (25^{th} and 75^{th} percentiles).

Table 3. Independent predictors of all-cause mortality

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age* (per 1 year)	1.063	1.052-1.075	< 0.001	1.023	1.008-1.038	
Female*	1.746	1.359-2.244	< 0.001	0.944	0.666-1.354	
Diabetes mellitus*	1.868	1.451-2.404	< 0.001	1.384	1.004-1.907	
Hipertension*	1.708	1.329-2.196	< 0.001	0.999	0.719-1.390	
Stroke history*	3.097	1.799-4.799	< 0.001	1.954	1.193-3.200	
History of CAD*	1.780	1.380-2.294	< 0.001	1.113	0.804-1.542	
HF or LVEF < 40*	2.525	1.944- 3.280	< 0.001	0.812	0.395-1.669	
Multivessel disease	1.918	1.500-2.451	< 0.001	1.393	1.067-1.818	0.015
Killip class ≥ 2	3.946	2.852-5.460	< 0.001	3.202	2.256-4.544	< 0.001
LVEF* (per 1% change)	0.957	0.946-0.969	< 0.001	0.972	0.958-0.986	
Hemoglobin (per 1 mg/dL)	0.803	0.760-0.848	< 0.001	0.887	0.816-0.965	
Creatinine# (mg/dL)	1.279	1.164-1.405	< 0.001	1.063	1.024-1.103	
GFR# (mL/minute/1.73 m^2)	0.977	0.972-0.981	< 0.001	0.638	0.444-0.917	
B-blocker use at follow-up	0.594	-0.446-0.790	< 0.001	0.676	0.500-0.915	0.011
ACE-I/ARB use at follow-up	0.476	0.359-0.631	< 0.001	0.646	0.475-0.878	0.005
Statin use at follow-up	0.688	0.507-0.933	< 0.001	1.116		
CHA2DS2-VASC score	1.537	1.435-1.645	< 0.001	1.444	1.327-1.572	< 0.001
CIN	4.038	2.956-5.517	< 0.001	1.850	1.298-2.637	0.001

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 receptor blocker, HF: Heart failure.
* These parameters were not entered into the multivariate model, as they are included in the CHA2DS2-VASC score calculation.
# These parameters are not entered into the model in order to prevent multicollinearity.

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[17,18]. Each of CHA2DS2-VASc's components has prognostic importance for CAD. Advanced age is a significant risk factor for mortality[19]. Similarly, HT, DM, and heart failure has been shown to be a long-term prognostic indicator[20,21]. 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 UA or non-Q-wave myocardial infarction patients[22]. In our study, patients with high CHA2DS2-VASc scores 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[23,24]. The proportion of women was higher in patients with high CHA2DS2-VASc score and CIN. Therefore, this may have contributed to the high mortality rates in these patients.

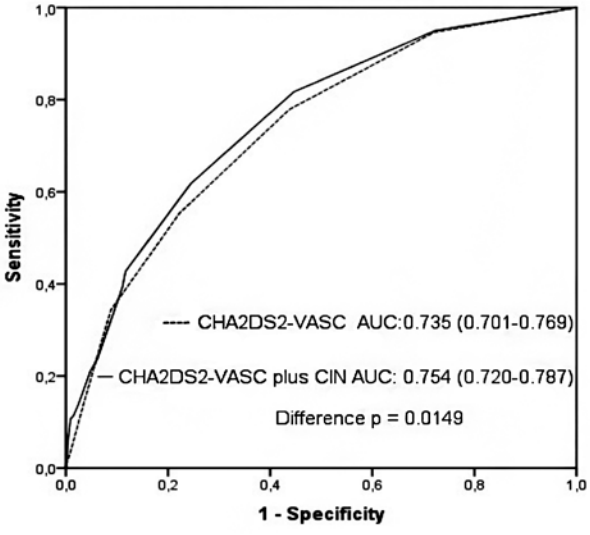

Figure 1. ROC analysis of CHA2DS2-VASc and CHA2DS2-VASc plus CIN.

Kim and colleagues have shown that the CHA2DS2-VASc score can be used to determine prognosis in acute myocardial infarction patients regardless of the presence of atrial fibrillation[25]. In this study, patients were divided into four groups according to their CHA2DS2-VASc scores. Patients with

high scores were older and female. Although in-hospital mortality was not different among the 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 with the CHA2DS2-VASc score was better able to predict all-cause mortality compared with the CHA2DS2-VASc score alone.

Serum creatinine levels have a significant prognostic value in ACS patients. It has been shown that baseline renal dysfunction was associated with a higher mortality rate 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, renin angiotensin-aldosterone system activation, and increased plasma levels of fibrinogen and homocysteine may contribute to the adverse outcomes 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 CAD proven by angiography was more frequent in these patients in our study. All these conditions may be related to adverse prognosis in patients with ACS[35].

Consequently, our findings might be correlated with well-known predictors, such as DM, HT, advanced age, heart failure, female gender, and renal dysfunction, with respect to cardiovascular mortality for ACS patients. Thus, these findings may explain why adding CIN to the CHA2DS2-VASc score 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 combining the CHA2DS2-VASc score 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 noninvasive 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 the CHA2DS2-VASc score improved the predictive value for all-cause mortality in these patients.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EA, DA

Analysis/Interpretation: OB, AD, AÇ, TK

Data Acquisition: EA, DA

Writting: TK, EA, AD

Critical Revision: TK, EA, DA, OB, AÇ

Final Approval: All of authors

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