ORIGINAL ARTICLE

Predictive value of ATRIA risk score for contrast-induced nephropathy after percutaneous coronary intervention for ST-segment elevation myocardial infarction

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SUMMARY

BACKGROUND: *The AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) risk score used to detect the thromboembolic and hemorrhagic risk in atrial fibrillation patients has been shown recently to predict poor clinical outcomes in patients with acute myocardial infarction (ACS), regardless of having atrial fibrillation (AF). We aimed to analyze the relationship between different risk scores and contrast-induced nephropathy (CIN) development in patients with ACS who underwent urgent percutaneous coronary intervention (PCI) and compare the predictive ability of the ATRIA risk score with the MEHRAN risk score.*

METHODS: *We analyzed 429 patients having St-segment Elevation Myocardial Infarction (STEMI) who underwent urgent PCI between January 2016 and February 2017. Patients were divided into two groups: those with and those without CIN and both groups were compared according to clinical, laboratory, and demographic features, including the CHA2DS2-VASc and ATRIA risk score. Predictors of CIN were determined by multivariate regression analysis. Receiver operating characteristics (ROC) curve analysis was used to analyze the prognostic value of CHA2DS2-VASc and ATRIA risk score for CIN, following STEMI.*

RESULTS: *Multivariate regression analysis showed that Athe TRIA risk score, Opaque/Creatinine Clearance ratio, and low left ventricular ejection fraction was an independent predictor of CIN. The C-statistics for the ATRIA risk score and CHA2DS2-VASC risk score were 0.66 and 0.64 ($p<0.001$, and $p<0.001$), respectively. A pair-wise comparison of ROC curves showed that both scores were not inferior to the MEHRAN score in predicting CIN.*

CONCLUSION: *The ATRIA and CHA2DS2-VASC scoring systems were useful for detecting CIN following STEMI.*

KEYWORDS: *ATRIA risk score, St-segment Elevation Myocardial Infarction, Contrast induced nephropathy*

RUNNING HEAD: *The relationship between ATRIA risk score and contrast induced nephropathy*

INTRODUCTION

Quick restoration of coronary blood flow in an occluded coronary artery is the fundamental aim of early ST-elevation myocardial infarction (STEMI) therapy. Primary percutaneous coronary intervention (p-PCI) is the preferred reperfusion strategy for acute STEMI patients within the first few hours after the onset of symptoms.[1] However, life-threatening complications such as contrast-induced nephropathy (CIN) can be seen after p-PCI. A strong correlation between CIN and high mortality and morbidity in patients with STEMI has been shown. Additionally, these patients tend to have a long duration of hospitalization.[2,3] It was shown that different clinical and laboratory variables such as contrast media volume,

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presence of diabetes mellitus, chronic congestive heart failure, anemia and decreased renal perfusion were associated with CIN development.[4] Patients at high risk of CIN should be administered with early prophylactic measures such as hydration to prevent CIN. Additionally, high-risk patients should be followed up for creatinine progression after the procedure.[2] Therefore, scoring systems should be developed to predict the development of CIN.

The CHA2DS2-VASc and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) risk scores are cheap and easy scoring systems used to predict the risk of thromboembolism in non-valvular atrial fibrillation (AF) patients.[5,6] Additionally, these scoring systems have been shown to accurately predict worse clinical outcomes in patients with acute coronary syndrome regardless of having AF. [7,8] Moreover, we showed that the CHA2DS2-VASC score has predicted AF following STEMI and associated with epicardial fat tissue. [9,10] The components of these scoring systems, such as advanced age, presence of hypertension, presence of diabetes mellitus, low ejection fraction, and female gender have been associated with poor outcomes, including recurrent ischemic events.[7,11]

In this study, we aimed to investigate the predictive value of different thromboembolic risk scores in atrial fibrillation for the development of CIN.

METHODS

Study population

This was a prospective single-center study. The overall study population included 459 patients undergoing primary percutaneous coronary intervention diagnosis of ST-elevation myocardial infarction. The exclusion criteria included hyperthyroidism (5 patients), age <18 years, end-stage renal failure (10 patients), patients treated with emergent coronary artery bypass graft surgery (10 patients), sepsis (5 patients), exposed to contrast injection within 7 days before primary percutaneous coronary intervention (30 patients), known malignancy, severe hepatic dysfunction, and inflammatory disease. Patients who presented with cardiogenic shock or died during the first 72 hours of their hospital stay, or during revascularization, were also excluded from the study. Therefore, the final study cohort consisted of 399 patients with STEMI. The study protocol was reviewed and approved by the Local Ethics Committee of the Süleyman Demirel University Medical School (Approval number: 72867572.050.01.04-299118) in accordance with the Declaration of Helsinki.

Diagnosis of contrast-induced nephropathy

CIN was defined as the impairment of renal function and measured as either a 25% increase in serum creatinine from the baseline or a 0.5 mg/dL increase in the absolute value when there was no alternative etiology within 72 hours of the first procedure[4]. Creatinine Clearance was calculated using the Cockcroft-Gault Equation.[12]

Diagnosis of thromboembolic risk

The CHA_2DS_2-VASc risk score is calculated by assigning a score of 1 point for each of the following conditions: congestive heart failure (ejection fraction< 40%), hypertension, age between 65 and 74 years, diabetes mellitus, vascular disease (myocardial infarction or peripheral arterial disease), and female gender; a score of 2 points for the following conditions: history of stroke or transient ischemic attack (TIA) and age > 75 years. The score is then used to predict the risk of thromboembolism in non-valvular AF patients. [5]

The ATRIA score was developed from the ATRIA study cohort and calculated using the following: anemia (hemoglobin <13 g/dL in men and <12 g/dL in women) (3 points), severe renal disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2) (3 points), age ≥75 years (2 points), prior bleeding, and hypertension. An ATRIA score of 0 to 3 is defined as "low risk," a score of 4 is defined as "intermediate risk," and a score ≥5 is defined as "high risk".[6]

Diagnosis of STEMI

Diagnoses were recorded by the participating physicians based on clinical, electrocardiographic and biochemical (elevated troponin levels) criteria. The type of myocardial infarction (ST-elevation vs. non-ST-elevation) and unstable angina were homogeneously defined based on current guidelines. All patients were treated according to the currently available guidelines. Primary percutaneous coronary intervention (PCI) was performed in all patients. [13]

Blood sampling

Blood samples were drawn from the antecubital vein by careful venipuncture using a 21 G sterile syringe without stasis between 08.00–10.00 AM after

a fasting period of 12 h. Glucose, creatinine, and lipid profiles were determined by standard methods. Hemogram parameters were measured in a blood sample collected in dipotassium EDTA tubes (Vacuette). An automatic blood counter (Beckman-Coulter Co, Miami, FL, USA) was used for whole blood counts.

STATISTICAL ANALYSIS

SPSS version 16.0 software package was used for statistical analyses in this study. Categorical variables were expressed as frequency (%) and compared using the $\chi 2$ test. Kolmogorov-Smirnov test was used to test the distribution of numeric variables; those with normal distribution were expressed as mean ± standard deviation and compared with Student's t-test. Data without normal distribution were expressed as median (Inter-quartile range (IQR) of 25%-75% percentiles) and compared with the Mann-Whitney U test. In all statistical analyses, a p-value <0.05 was considered statistically significant. The correlations between the CHA2DS2-VASc and ATRIA risk scores, CIN and other clinical, laboratory, and echocardiographic parameters were measured by Pearson or Spearman correlation analysis when appropriate. Univariate analysis and backward conditional binary logistic regression were performed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for the prediction of CIN. Receiver operating characteristics (ROC) curve analysis was used to analyze the prognostic value of the CHA2DS2-VASc and ATRIA risk scores for CIN, following STEMI. C-Statistic (area under the curve) was presented as a unified estimate of sensitivity and specificity according to the cutoff value that was obtained by the ROC curve analysis. The optimal cutoff value was defined as the value yielding the maximal Youden index, or the best-combined sensitivity and specificity.[14] All ROC comparisons were performed using the DeLong test. [15] C-Statistic (area under the curve) was presented as a unified estimate of sensitivity and specificity.

RESULTS

A total of 399 patients (mean age: 63±11 years; range, 28–91 years) were included in this study. During the follow-up period, 88 patients (22 %) developed CIN. The demographic and clinical characteristics of the patients with and without CIN are listed in Table 1. The patients with CIN were significantly older and more often female when compared to the patients without CIN (p< 0.001 and p= 0.015, respectively). Diabetes mellitus, hypertension, obesity, and hyperlipidemia rates were similar between patients with and without CIN (for all parameters p> 0.05). There were no statistically significant differences between patients with and without CIN with regards to cholesterol parameters (for all parameters p> 0.05). Left ventricle ejection fraction was significantly lower in patients with CIN than in patients without CIN (p= 0.016). Initial creatinine levels were similar between patients with and without CIN, but the 72-hour creatinine levels were higher in patients with CIN than in patients without CIN (p< 0.001)

The incidence of previous use of renin-angiotensin system (RAS) blockers was lower in patients with CIN than in patients without CIN (p= 0.055). There were no statistically significant differences between patients with and without CIN with regards to the use of beta-blockers, acetylsalicylic acid, clopidogrel, or statins. Among in-hospital treatments, the use of RAS blockers was lower in patients with CIN (p= 0.003), but other medications were similar among patients with and without CIN (p> 0.05). Patients with CIN had a longer period of stay at the Coronary Care Unit and a longer follow-up duration than patients without CIN (2.2± 0.7 versus 2.0± 0.4; p= 0.02 and 6.0 ± 2.2 versus 5.1 ± 1.7; p < 0.001, respectively).

The mean CHA2DS2-VASc, ATRIA, and MEHRAN scores were significantly higher in patients with CIN than in patients without CIN (2.6 ± 1.4 versus 1.9 ±1.4, p< 0.001; 4.3 ±2.7 versus 3.1 ± 2.7, p< 0.001; 5.3± 2.7 versus 4.3 ± 2.7, p< 0.001; respectively).

Prediction of Contrast-induced nephropathy

Univariate analyses showed that high CHA2DS2-VASc and ATRIA risk scores, low left ventricle ejection fraction, advanced age, opaque amount, opaque amount/Creatinine Clearance ratio, and female gender were significantly associated with a higher risk of development of CIN (Table 2). On the other hand, pre and in-hospital use of RAS blockers were inversely associated with the risk of incident CIN (Table 2).

A multivariate binary logistic regression analysis was carried out, including all characteristics that were associated with the development of CIN in the univariate analysis. This analysis showed that the opaque amount/Creatinine Clearance ratio (OR: 1.22; 95 % CI: 1.00-1.50, p= 0.04), ATRIA score (OR: 1.12; 95 % CI: 1.00-1.25, p= 0.04) and left ventricle ejection

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH AND WITHOUT CONTRAST-INDUCED NEPHROPATHY

	Contrast-Induced Nephropathy		
	No (n=311)	Yes (n=88)	P-value
Female gender n, (%)	59 (19.9)	28 (31.8)	0.015
Diabetes Mellitus n, (%)	71 (23.9)	27 (30.7)	0.127
Hypertension n, (%)	142 (47.8)	48 (54.5)	0.161
Hyperlipidemia n, (%)	57 (19.2)	19 (21.6)	0.360
Age (years)	61.4 ± 13	67.9 ±9	< 0.001
Previous treatment			
RAS blockers n, (%)	45 (15.2)	7 (8.0)	0.055
B Blockers n, (%)	47 (15.8)	10 (11.4)	0.127
Statins n, (%)	31 (10.4)	10 (11.4)	0.469
In hospital Treatment			
RAS blockers n, (%)	248 (83.5)	61 (69.3)	0.003
B Blockers n, (%)	275 (92.6)	86 (97.7)	0.07
Statins n, (%)	292 (98.3)	87 (98.9)	0.585
Left ventricle ejection fraction (%)	45.8 ± 9.5	42.5 ± 10	0.016
CHA2DS2-VASc Risk score	1.9 ±1.4	2.6 ± 1.4	< 0.001
ATRIA Risk Score	3.1 ± 2.7	4.3 ± 2.7	< 0.001
Opaque amount (cc)	124 ± 38	169 ± 44	< 0.001
Opaque/CrCl ratio	1.9 ± 1.3	2.8 ± 1.4	< 0.001
Mehran Risk Score	4.3 ± 3.7	5.3 ± 2.7	< 0.001
Initial creatinine (mg/dl)	1.1 ± 0.3	1.0 ± 0.2	0.168
72th hour creatinine (mg/dl)	1.1 ± 0.3	1.5 ± 0.5	< 0.001
Duration of CCU stay (day)	2.0 ± 0.4	2.2 ± 0.7	0.02
Total Hospitalization stay (day)	5.1 ± 1.7	6.0 ± 2.2	< 0.001

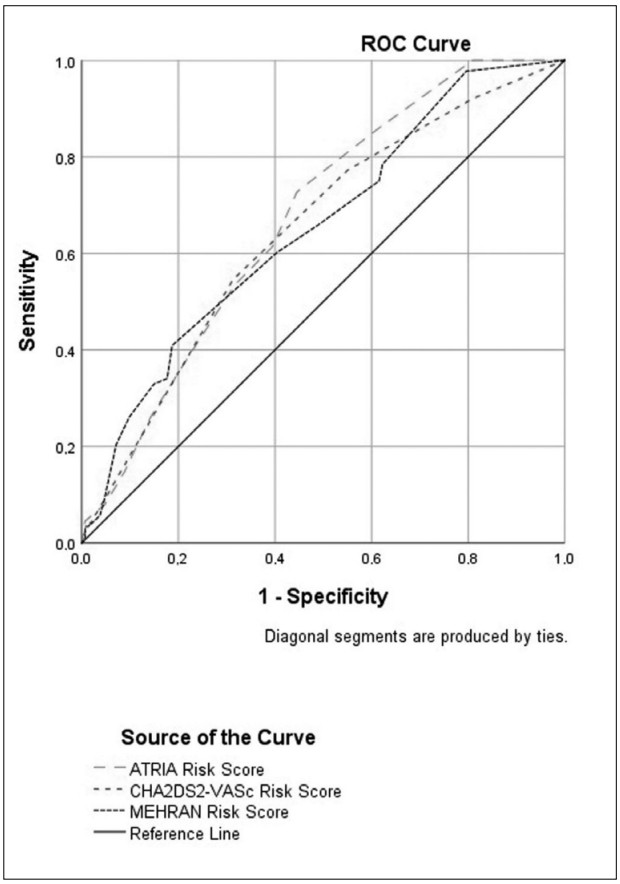
Data presented as mean ± standart deviation or number (%) of patients. Abbreviations: RAS = renin-angiotensin system; CHA2DS2-VASc= congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke, vascular disease, age 65 to 74 years, female gender; ATRIA - Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; CrCl: Creatinine Clearance, CCU: Coronary care unit

TABLE 2. UNIVARIATE AND MULTIVARIATE REGRESSION ANALYSIS OF PREDICTORS OF CONTRAST-INDUCED NEPHROPATHY IN THE STUDY POPULATION.

	Unadjusted Odds Ratio	Confidence interval	P-value	Adjusted Odds Ratio	Confidence interval	P-value
Female gender	1.88	1.1-3.2	0.02			
Left ventricle ejection fraction	0.96	0.94-0.99	0.007	0.97	0.95-1.00	0.09
Previous ACEi using	2.0	0.89-4.76	0.08			
In-hospital ACEi using	2.2	1.29-3.87	0.004			
CHA2DS2-VASc Risk score	1.3	1.17-1.63	< 0.001			
High CHA2DS2-VASc group	2.7	1.57-4.70	< 0.001			
ATRIA Risk Score	1.16	1.07-1.27	< 0.001	1.12	1.00- 1.25	0.04
Opaque amount	1.024	1.01-1.03	< 0.001			
Opaque/CrCl ratio	1.44	1.22-1.70	< 0.001	1.22	1.00-1.50	0.04
Mehran Risk Score	1.13	1.06-1.20	< 0.001			

fraction (OR: 0.97; 95 % CI: 0.95-1.00, p= 0.09) remained as independent factors for CIN development (Table 3). the ROC curve analysis showed that both ATRIA (C-statistic: 0.66; 95% CI: 0.61-0.71, p< 0.001) and CHA2DS2-VASc scores (C-statistic: 0.64; 95% CI: 0.59-0.76, p< 0.001) were significant predictors of CIN following STEMI (Figure 1) We calculated that a cut-off point of 2 for ATRIA and CHA2DS2-VASc scores could estimate the presence of CIN with a sensitivity of 72% and 55% and a specificity of 54% and 68%, respectively. Additionally, the ROC curve analysis showed that the opaque amount/Creatinine

FIGURE 1. ROC CURVE WITH CALCULATED AREA UNDER THE CURVE AND OPTIMAL CUT-OFF POINT FOR THE CHA2DS2-VASC SCORE AND ATRIA SCORE TO IDENTIFY THE PRESENCE OF CIN.



Clearance ratio (C-statistic: 0.70; 95% CI: 0.66-0.75, p<0.001) was a significant predictor of CIN following STEMI. We performed a pair-wise comparison of ROC curves, and recorded that the predictive value of the ATRIA risk score with regard to CIN development was similar to that of the MEHRAN risk, CHA2DS2-VASc, and ATRIA risk scores (by DeLong method, AUC ATRIA vs. AUC MEHRAN z test= 0.712, p= 0.476; AUC ATRIA vs. AUC CHA2DS2-VASc z test= 0.813, p= 0.07; AUC MEHRAN vs. AUC CHA2DS2-VASc z test= 0.238, p= 0.812)

DISCUSSION

The current study showed that higher CHA2DS2-VASc and ATRIA scores were independently associated with the development of CIN in STEMI patients treated with p-PCI; consequently, both scores could be helpful and appropriate scoring systems for predicting CIN after STEMI treated with p-PCI. Additionally, the opaque amount/Creatinine Clearance ratio is a powerful predictor of CIN development.

CIN is a serious complication of p-PCI after STEMI and is associated with worse clinical outcomes, such as prolonged length of hospital stays, rising costs, and increased short- and long-term morbidity and mortality.[2,3] It is important to anticipate which patients may develop CIN. There are several risk scores that have been established to predict CIN development.[4,16,17] The MEHRAN score, created for predicting CIN,[4] includes physical examination, laboratory tests, and various demographic and angiographic parameters. Additionally, Gurm et al.[16] defined a new model for predicting CIN after PCI. However, similar to the MEHRAN score, this score is complex and time-consuming as it also requires clinical and laboratory variables that may not be available to the clinician immediately. Therefore, these scoring systems are confusing and impractical due to their plurality and lack of ease of use. Conversely, the CHA2DS2-VASc and ATRIA scores are simple and easy scoring systems and may be used for predicting CIN in patients with STEMI before the procedure.

Although the underlying mechanisms of CIN are not entirely understood [18,19], previous studies have shown that renal vasoconstriction, endothelial dysfunction, and endothelial damage contribute to the process of CIN development by renal tubular injury and medullary hypoxia.[20] Diabetes mellitus, hypertension, advanced age, congestive heart failure, volume depletion, myocardial infarction, renal dysfunction are the most important risk factors for CIN development. [4,21-23] The risk factors of CIN are similar to the components of the CHA2DS2-VASc and ATRIA risk scores.[4] Furthermore, these scores can be used to predict the risk of CIN. Kurtul et al [8] showed that the CHA2DS2-VASc score can be used as a simple and useful tool for predicting CIN in patients with acute coronary syndrome (ACS). The data of the current study corroborate the results of Kurtul et al. Additionally, we showed that the ATRIA score can also be used to predict CIN following STEMI. Moreover, not only was the ATRIA score more powerful than the CHA2DS2-VASc score in predicting CIN, it was found to be non-inferior to the MEHRAN score in predicting CIN.

In the present study, female gender, low ejection fraction, opaque amount, opaque/eGFR ratio were risk factors for the development of CIN. Previous studies have also shown similar results. [8,24,25] Contrast volume and basal renal insufficiency are important risk factors for CIN;[19] accordingly, the

opaque/eGFR ratio is a good indicator for CIN.[25] Our study also indicated that opaque/eGFR ratio was a powerful predictor of CIN development.

Patients at high risk of CIN should be managed with early additional measures to prevent CIN. Although there are different established scoring systems to predict CIN risk, most of these include clinical, biological, and variables that can only be obtained after invasive interventions not available pre-procedure. However, the ATRIA and CHA2DS2-VASc scoring systems can be evaluated at the first contact with a physician. Additionally, measures such as hydration may be administrated to high-risk patients, who also should be followed up for creatinine progression after the procedure.

Importantly, this study has some limitations. First, it had a relatively small sample size and engaged in a single-center experience. Second, we have only estimated our model performance in a derivation cohort, while data for a confirmation cohort are lacking. Third, we did not follow up with major adverse cardiovascular events data. Our results should, therefore, be verified by future multi-center prospective longitudinal studies with larger sample sizes. The limitations of this study should be considered while interpreting these results.

CONCLUSION

We have shown in the current study that the ATRIA and CHA2DS2-VASc scoring systems were useful for detecting CIN following STEMI. Additionally, when the ATRIA risk score was compared with previously well-validated scores, it was found to be similar in power for predicting the development of CIN. Patients at high risk, according to the ATRIA and CHA2DS2-VASc scoring systems, should be followed up for creatinine progression after the procedure and administrated intravenous hydration before the procedure.

RESUMO

OBJETIVO: *O escore Anticoagulação e Fatores de Risco na Fibrilação Atrial (Atria), usado na detecção do risco tromboembólico e hemorrágico de pacientes com fibrilação atrial (FA), recentemente demonstrou predizer resultados clínicos ruins em pacientes com infarto agudo do miocárdio (SCA), independentemente de ter FA. Nosso objetivo foi analisar a relação entre os diferentes escores de risco e o desenvolvimento de nefropatia induzida por contraste (NIC) em pacientes com SCA submetidos à intervenção coronária percutânea (ICP) urgente e comparar a capacidade preditiva do escore de risco Atria com o escore de risco Mehran.*

MÉTODOS: *Foram analisados 429 pacientes com infarto agudo do miocárdio com elevação do segmento ST (IAM-ST) submetidos à ICP de urgência entre janeiro de 2016 e fevereiro de 2017. Os pacientes foram divididos em dois grupos: aqueles com e sem NIC, e ambos os grupos foram comparados de acordo com as características clínicas, laboratoriais e demográficas, incluindo os escores de risco CHA2DS2-VASc e Atria. Preditores de NIC foram determinados por análise de regressão multivariada. A análise da curva características de operação do receptor (ROC) foi utilizada para analisar o valor prognóstico dos escores de risco CHA2DS2-VASc e Atria para NIC, após IAM-ST.*

RESULTADOS: *A análise de regressão multivariada mostrou que o escore de risco Atria, a relação opaca/crCl e a baixa fração de ejeção do ventrículo esquerdo foram preditores independentes de NIC. A estatística-C para o escore de risco Atria e o escore de risco CHA2DS2-VASC foi de 0,66 e 0,64 (p<0,001 e p<0,001), respectivamente. Uma comparação de pares de curvas características de operação do receptor mostrou que ambos os escores foram não inferiores ao escore Mehran na previsão de NIC.*

CONCLUSÃO: *Os sistemas de pontuação Atria e CHA2DS2-VASC foram sistemas úteis para a detecção de NIC após IAM-ST.*

PALAVRAS-CHAVE: *Escore de risco Atria. Infarto do miocárdio com elevação do segmento ST. Nefropatia induzida por contraste.*

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