Two Statistical Methods to Analyze the Role of CHA2DS2VASc Score in Patients with STEMI

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Abstract: - The CHA2DS2VASc score includes risk factors for coronary artery disease. The aim of this study is to show that the CHA2DS2VASc score calculated at the time of hospital admission may predict mortality and major adverse cardiovascular and cerebrovascular events (MACCE) in-hospital and at 30-day follow-up for patients with STEMI, who were subjected to primary percutaneous coronary intervention (p-PCI). A retrospective cohort study was performed at University Hospital Center 'Mother Teresa', in the Cardiology Department between June 2021 and September 2021. The CHA2DS2VASc score was calculated at the time of hospital admission for all of them. The study population was divided into 3 groups according to the CHA2DS2VASc score at the time of admission. A statistical control of result of hospital MACCE was done. As the result of multivariable analysis, smoking and CHA2DS2VASc groups were found to be independent MACCE predictors. The chances of developing MACCE were approximately 5 times higher in a patient of the third CHA2DS2VASc group, compared to that of the first group. CHA2DS2VASc groups are important to define the likelihood that MACCE will occur in patients with ascending STEMI who had undergone PCI. The ROC plot provided a visual representation of the accuracy of CHA_2DS_2VASc in predicting reinfarction and stroke. AUC 0.852 (95% C.I: 0.776-0.928) showed when CHA2DS2VASc has this predictive ability for morbidity and mortality. CHA2DS2VASc ≥ 4 can be used to determine risk of reinfarction and stroke.

Key-Words: - AUC, CHA_2DS_2VASc, MACCE, Multiple logistics model, ROC, STEMI

Received: August 24, 2021. Revised: May 16, 2022. Accepted: June 5, 2022. Published: July 1, 2022.

1 Introduction

The CHA2DS2VASc score is a well know method capable of predicting the risk of stroke in patients with atrial fibrillation (AF) [1]. Recent research has extended the use of CHA2DS2VASc score to non-AF populations [1]. Previous studies have demonstrated that the CHA_2DS_2VASc score can predict in-hospital and long-term adverse clinical outcomes, including mortality in stable coronary artery disease (CAD), as well as an acute coronary syndrome. A CHA2DS2VASc >2 [3] was an independent predictor for the incidence of acute stent thrombosis. The score includes variables such as heart failure, hypertension (HT), older age, diabetes mellitus (DM), female gender [4], vascular disease, and stroke. The components have similar risk factors, and as such are valued at 1 point, with the exception of age (65<Age <75 = 1 point, Age > 75 = 2 points) [5] and previous stroke/transient ischemic attack (2 points) [6]. Since these components are also risk factors for atherosclerosis and ischemic heart disease, it may be reasonable to use them for risk stratification in patients with STEMI [7], too. The CHA2DS2VASc scoring system is easy to calculate, so it may be useful compared to other scores such as GRACE [8][8], and TIMI 0 that cannot be calculated manually. Since acute myocardial infarction (AMI) is considered to be a vascular disease, all patients with AMI received at least 1 point.

2 Statistical Analysis

The data were processed in SPSS version 26.0 for Windows (IBM, USA). During the study, the continuous numerical variables were descriptively analysed. The mean, standard deviation, and even the confidence interval (CI) of mean with a confidence level of 95% of all these data were represented. CI generates the upper bound "Upper Confidence Level", UCL, and the lower "Lower Confidence Level", LCL. The ANOVA method was used to compare the means of continuous random variables, or binary random variables. The p-value of ANOVA simply indicates whether these averages are equal or not. The comparison of the values of more than two groups was also done with the Benjamin-Hochberg method. This method is suitable for testing the hypothesis of equal mean values in these cases because it controls which one differs. It works with two values of Type I error, α = 0.05 and 0.01. When the letters shown below the averages are capitalized then the p-value was less than 0.01, the difference between the groups is very significant. When the group letters below the

averages are in lower case, then 0.01 < p-value < 0.05, meaning that the difference between the groups is significant. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of CHA2DS2VASc score or the value of CHA2DS2VASc scores needed to predict the development of MACCE.

3 Materials and Methods

212 consecutive patients, included in this study, are admitted to undergoing Primary PCI for ST-elevated myocardial infarction (STEMI) in the Cardiology Center of the "Mother Teresa" University Medical Center, (177 men and 35 women with a mean age of 63.82, range: 30-85 y.). STEMI was diagnosed based on ST-segment elevation ≥1 mm in at least 2 contiguous electrocardiographic (ECG) leads or new left bundle branch block with chest pain lasting over 30 minutes. Blood samples were taken at the time of admission to the hospital and daily during the hospital stay. A 12-lead ECG was recorded in each patient immediately upon admission to the hospital, and myocardial infarction (MI) type is observed with the help of ECG. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson method.

Follow-up procedures took place 1 month after discharge, using a standardized protocol that included telephone contacts, and recordings of cardiac events. The primary endpoint was all-cause mortality in hospital. Cardiovascular deaths, re-infarctions, and repeated target vessel revascularizations (TVRs) were defined as MACCE. During short-term follow-up, any events of stroke, heart failure-related re-hospitalizations, or MACCE were noted. The potential occurrence of MACCE was calculated based on data gathered from phone call conversations with each patient 1 month after discharge. If we could not reach the patient, the patient's general practitioner was contacted In cases of patients with a possible MACCE or unknown status, the electronic hospital records were investigated. All information possibly indicating MACCE was further investigated by examining medical records from the hospital and/or the general practitioner. All potential events were then reviewed by two independent cardiologists, who decided whether MACCE occurred or not. Both cardiologists were blinded for the GRACE, TIMI, and CHA_2DS_2-VAS scores.

Patients were divided into three groups according to their CHA_2DS_2VAS scores. Patients with scores of 1-2 were categorized in the low-level CHA2DS2VASc group (1), those of 3-4 points in the medium-level group (2), while the high-level of CHA2DS2VASc group (3) included patients with the highest scores of CHA_2DS_2VASc, ranging from 5 to 9 [11].

Demographic and clinical data of the patients are registered in a dedicated database. Then these characteristics of the studied population were analyzed. 64 patients were in the low-level CHA2DS2VASc group (No. 64 males/0 female), 112 in the medium-level group (No. 94 males/18 females), and 36 patients in the high-level group (No. 19 males/17 females). The average age of patients of the low-level group of CHA2DS2VASc was 55 years; that of the medium-level group was 66 years for males and 61 for females; that of the high-level group was 77 years for males and 75 for females as detailed in

Table 1. In the different CHA2DS2VASc groups, age increased significantly (F-value = 73,489 and p-value = 6.7849E-45). The first group is younger, averaging 55.45, the second at 64.8, and the third at 75.61. As expected, HTN, DM, Stroke, and CHF occurred more often in patients with the high-level CHA2DS2VASc. We noted the difference between Killip Class and CHA2DS2-VAS groups, as there are cases of patients of different groups of CHA2DS2VASc in every classification of Killip Class.

Table 1. The main characteristic of patients

		low-level group CHA2DS2VASc		medium-level group CHA2DS2VASc		high-level group CHA2DS2VASc	
		(A)		(B)		(C)	
		Count	Column N %	Count	Column N %	Count	Column N %
Sex	male	64	100.0%	94 C	83.9%	19	52.8%
	female	0	0.0%	18	16.1%	17 B	47.2%
Dyslipidemia		32	50.0%	63	56.3%	17	47.2%
HTN		45	70.3%	108 A	96.4%	35 A	97.2%

DM		3	4.7%	66 A	58.9%	27 A	75.0%
Stroke		0	0.0%	1	0.9%	10 B	27.8%
CHF		0 B C	0.0%	3	2.7%	2	5.6%
PAD		0	0.0%	0	0.0%	0	0.0%
Post-IM		1	1.6%	5	4.5%	4	11.1%
Post CABG		0	0.0%	0	0.0%	0	0.0%
Post PCI		3	4.7%	6	5.4%	3	8.3%
Killip Class	I	52 B C	81.3%	74 C	66.1%	13	36.1%
	II	11	17.2%	30	26.8%	19 A B	52.8%
	III	1	1.6%	6	5.4%	3	8.3%

All laboratory assessments were stored in the institutional, in this dedicated laboratory database, too. Procedural and angiographic data were prospectively collected and entered by interventional cardiologists and specialized nurses. The results of angiographic and procedural data are represented in Table 2.

By using the Benjamin-Hochberg method, significant changes were shown only in terms of the number of afflicted vessels. The number of patients in the second and third groups of CHA2DS2VASc with 3-vessel CAD was significantly higher than in the first CHA2DS2VASc group. The other procedural and angiographic data have no statistically significant difference.

Table 2. Angiography and procedural characteristics of patients

		low-level group CHA2DS2VASc (A)		medium-level group CHA2DS2VASc (B)		high-level group vesselCHA2DS2VASc (C)	
		N	%	N	%	N	%
Stent DES	1	26	40.6%	53	47.3%	16	44.4%
Stent BMS	1	40	62.5%	65	58.0%	23	63.9%
STEMI Anterior	1	28	43.8%	51	45.5%	18	50.0%
Inferior	1	26	40.6%	47	42.0%	17	47.2%
Inferior-lateral	1	7	10.9%	12	10.7%	1	2.8%
Posterior	1	2	3.1%	1	0.9%	0	0.0%
Lateral	1	1	1.6%	1	0.9%	0	0.0%
TIMI Flow	0	0	0.0%	1	0.9%	0	0.0%
	1	1	1.6%	3	2.7%	1	2.8%
	2	6	9.4%	13	11.6%	6	16.7%
	3	57	89.1%	95	84.8%	29	80.6%
CAD 1-Vesssel	1	27	42.2%	28	25.0%	9	25.0%
2- Vesssel	1	25	39.1%	45	41.1%	11	30.6%
3- Vesssel	1	12	18.8%	38 a	33.9%	16 a	44.4%
Culprit vessel		64		112		36	
LAD	1	28	43.8%	51	45.5%	18	50.0%
RCA	1	25	39.1%	46	41.1%	17	47.2%
LCX	1	9	14.1%	14	12.5%	1	2.8%
D1	1	0	0.0%	1	0.9%	0	0.0%
MI	1	2	3.1%	0	0.0%	0	0.0%
VSG	0	64	100.0%	112	100.0%	36	100.0%

When analyzing laboratory baseline data, significant changes were observed in variables: creatinine, Hb, and glucose in different CHA2DS2VASc groups.

Table 3 presents the averages of creatinine, Hb, and glucose in each of the CHA2DS2VASc groups but also the 95% confidence intervals where these

averages are located (respectively LCL and ULC). Creatinine increased only in the third group of CHA2DS2VASc, Hb decreased significantly throughout the three levels of CHA2DS2VASc,

while glucose displayed an increase in the two higher levels.

Table 3. Laboratory data

	low-level group CHA2DS2VASc (A)			medium-level group CHA2DS2VASc (B)			high-level group CHA2DS2VASc (C)		
	Mean	LCL	UCL	Mean	LCL	UCL	Mean	LCL	UCL
Creatinine (mg/dl)	.98	.93	1.02	1.03	.99	1.08	1.12 A B	1.04	1.20
Hb (g/dl)	13.63 BC	13.32	13.94	12.94 C	12.69	13.20	11.91	11.33	12.48
Glucose(mg/dl)	126.33	116.95	135.70	178.89 A	166.14	191.65	181.50 A	157.57	205.43

The hospitalization time varied from 1 to 20 days. The average length of stay (ALOS) in a hospital was 5.444, [5.444 ± 0.36]. In 50% of cases, the stay time was 4-7 days. There was no statistical difference in the hospitalization time between the CHA2DS2VASc groups.

Table 4 shows the therapy of patients during hospitalization. During the in-hospital treatment, a greater use of diuretics, nitrates, and positive inotropes (Dobutamine, Dopamine, and Noradrenaline) was noticed in the third group of CHA2DS2VASc.

Table 4. In-hospital therapy

	low-level group CHA2DS2VASc (A)		medium-level group CHA2DS2VASc (B)		high-level group CHA2DS2VASc (C)	
	N	%	N	%	N	%
DAPT	641	100.0%	1121	100.0%	361	100.0%
Statin	641	100.0%	1121	100.0%	361	100.0%
B- blockers	61	95.3%	106	94.6%	32	88.9%
ACE-I/ARB	62	96.9%	107	95.5%	34	94.4%
Diuretics	20	31.7%	50	44.6%	21 a	58.3%
Antiarrhythmics						
Nitrates						
Inotrop+	2	3.1%	6	5.4%	4	11.1%
	13	20.3%	34	30.4%	19 A b	52.8%
	01	0.0%	3	2.7%	6 B	16.7%

As a result of dividing the patients into three groups, the likelihood of morbidity was recorded at 3.1% in the low-level group of CHA2DS2VASc, 12.5% in the medium-level group, and 52.8% in the high-level one. When analyzing survival data of MACCE 30 days after discharge, it was concluded that the survival probability for patients had increased from one CHA2DS2VASc group to another (p-value <0.01). The survival curves 0, 0 were plotted using the Kaplan Meier method (Figure1). The Survival Function Graph of Cardiovascular Problems for the three levels of CHA2DS2VASc serves to define the point estimation of the probability that patients do not show problems in a certain period of time after surgery. The result of Long-Rank, (Chi-Square =44.177, p-value= 2.5538E-10), and two other methods: Breslow (Generalized Wilcoxon), (Chi-Square =44.699, p-value= 2E-10) and Tarone-Ware (Chi-Square =44.449, p-value= 2E-10), indicate that likelihood of MACCE differ among CHA2DS2VASc groups at many points during the study.

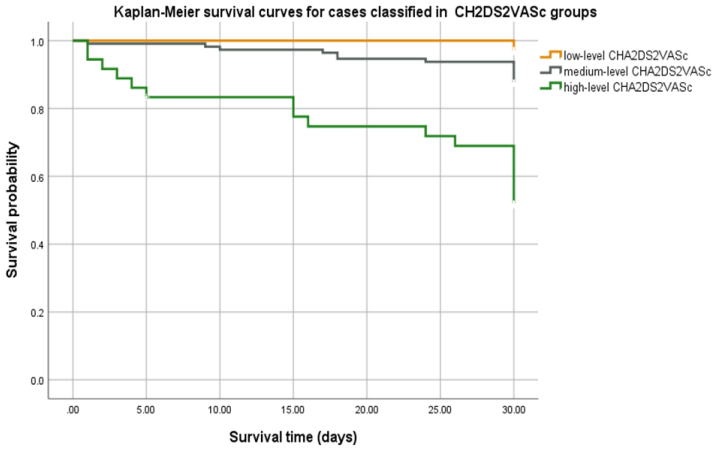

Fig. 1: Kaplan- Meier survival curves for cases classified into groups

To study the relationship of MACCE and independent variables age, gender, HTN, DM, and CHA2DS2VASc groups, we have used logistic regression. The multiple logistics model of MACCE, represented in Table 5, shows the significant impact CHA2DS2VASc -groups (p-value 0.02) and smoking (p-value 0.034) have in the forecast of MACCE. The multiple logistics model 0 is fitting as long as the Hosmer and Lemeshow test result is Chi-square 5.191 and sig. 0.737. This model justifies 54% of the variation of MACCE. Furthermore, a patient from high-level CHA2DS2VASc -group has higher odds for MACCE compared to a patient from CHA2DS2VASc group 1, (4.939 times higher, p-value = 0.026).

Table 5. The multiple logistics model of MACCE Total

Variables in the Equation		B	ODD RATIO	P-Value
Step 1a	Age	.031	1.060	.303
	Sex	.466	.486	.486
	Smoking	1.362	4.503	.034
	HTN	-.392	.182	.669
	DM	.677	1.561	.212
	CHA2DS2VASc group (1)		7.829	.020
	CHA2DS2VASc group (2)	1.083	1.168	.280
	CHA2DS2VASc group (3)	2.926	4.939	.026
	Constant	-6.207	8.543	.003

a. Variable(s) entered on step 1: Age, Sex, Smoking, HTN, DM, score group.

A new variable, MACCE Total was created. This is a Bernoulli variable for patients that had problems such as stroke, re-infraction, thrombosis, anterior infarction, or death within 30 days after STEMI [15]. ROC curves were plotted (false positive rate versus sensitivity) and areas under the curve (AUC ROC) were calculated, aiming to determine optimal test cut-offs for the patients with STEMI [16]. In receiver operating characteristic curve analysis, the area under the curve, ROC, for predicting MACCE Total was 0.852 (p =3.155 E-6, 95% CI 0.776–0.928). The cut-off value for CHA2DS2VASc score was 4.5 (sensitivity 93.9%, specificity 76.2%), (Figure 2).

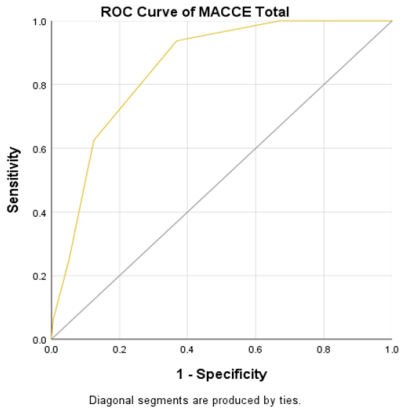

Fig. 2: ROC Curve of MACCE Total

4 Results

CHA2DS2VASc score is a basic, useful, and easily recalled bedside score for predicting in-hospital and short-term adverse clinical outcomes in STEMI. It is a good classification of morbidity and mortality in-hospital and in a short time follow-up, in those patients. In this study was shown that CHA2DS2VASc ≥ 4 can be used to determine the risk of reinfarction and stroke. Additionally, previous studies have suggested dividing the patients into two groups according to their CHA2DS2VASc score. The findings of the present study appear to agree with the idea of three CHA2DS2VASc groups as a strong and independent predictor of MACCE. These CHA2DS2VASc groups have the important advantage of identifying extremely low-risk patients with major adverse cardiovascular and cerebrovascular events, MACCE, as well as classifying a portion of patients as high risk. Using a different therapy for different CHA2DS2VASc groups (i.e. different antithrombotic therapy for each group, with greater use of reperfusion therapy for the high-level group), it is possible to decline in acute after STEMI. Detection of high creatinine or glucose in the high-level group may considerably influence the further treatment of the patients of this group.

The probabilities of MACCE differ among CHA2DS2VASc groups at many points throughout the first 30 days after discharge. They are approximately shown in Kaplan Meier survival curves of the three studied groups.

References:

[1] Ly Chen, L Norby, A Chamberlain, R. MacLehose, L. Bengtson L, P. Lutsey, and Alonso A, *CHA2DS2VASc Score and Stroke Prediction in Atrial Fibrillation in Whites, Blacks, and Hispanics. 2019;* https://doi.org/10.1161/strokeaha.118.021453

[2] GP Perna. *High CHA2DS2VASc score without atrial fibrillation: 'NAO yes, NAO no'.* European Heart Journal Supplements, Volume 21, Issue Supplement_B, March 2019, Pages B67–B68. 2019; https://doi.org/10.1093/eurheartj/suz011.

[3] KH Kim, W Kim, SH Hwang, Wy Kang, et al, *The CHA2DS2VASc score can be used to stratify the prognosis of acute myocardial infarction patients irrespective of the presence of atrial fibrillation.* Journal of cardiology, 65(2), 121–127. 2015; https://www.journal-of-cardiology.com/article/S0914-5087(14)00141-5/fulltext

[4] J Wei, T Henry, *Women Have a Worse Prognosis Than Men Following STEMI*: *CON*, American College of Cardiology. 2017; https://www.acc.org/latest-in-cardiology/articles/2017/12/20/07/04/women-have-a-worse-prognosis-than-men-following-stemi-con

[5] Mr O'Reilly, Ld McCullough, *Age and Sex Are Critical Factors in Ischemic Stroke Pathology*, Endocrinology, Volume 159, Issue 8, August 2018, Pages 3120 – 8131. 2018; https://doi.org/10.1210/en.2018-00465

[6] J Xu, S Jia, Zhu P Pei, L Jiang, P Jiang, Y Song, et al. *Does Prior Stroke Predict Long-Term Recurrent Stroke After Percutaneous Coronary Intervention? Five-Year Results from a Large Cohort Study* Front. Neurol., 2021; https://doi.org/10.3389/fneur. 2021.740136

[7] RA Weir, JJ McMurray, EJ Velazquez, *Epidemiology of Heart Failure and Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction*, The American Journal of Cardiology, 97(10), 13–25. 2006; https://www.ajconline.org/article/S0002-9149(06)00460-7/fulltext

[8] KA Fox, OH Dabbous, RJ Goldberg, KS Pieper, KA Eagle, et al, *Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE),* BMJ (Clinical research ed.), 333(7578), 1091. 2006; https://www.bmj.com/content/333/7578/1091

[9] G Sofidis, N Otountzidis, N Stalikas, et al., *Association of GRACE Risk Score with Coronary Artery Disease Complexity in Patients with Acute Coronary Syndrome.2021*, https://www.mdpi.com/2077-0383/10/10/2210

[10] D Morrow, E Antman, A Charlesworth, et al., *TIMI Risk Score for ST-Elevation Myocardial Infarction: A Convenient, Bedside, Clinical Score for Risk assess.2000;* circulation, 102(37), 2031–2037. https://www.ahajournals.org/doi/10.1161/01.CIR.102.17.2031

[11] B Hudzik, J Szkodziński, M Hawranek, A Lekston, et al., *CHA2DS2VASc score is useful in predicting poor 12-month outcomes following myocardial infarction in diabetic patients without atrial fibrillation*, Acta Diabetologica, 53(5), 807–815.2016; 2016, https://link.springer.com/article/10.1007/s00592-016-0877-6

[12] PG Karadeniz, I Ercan, *Examining tests for comparing survival curves with right-censored data*, Statistics in Transition. New Series, 18(2), 311–328. 2017 https://www.exeley.com/statistics_in_transition/doi/10.21307/stattrans-2016-072

[13] SJ Pocock, TC Clayton, DG Altman, *Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls*, The Lancet, 359(9318), 1686–1689.2002; https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)08594-X/fulltext

[14] A Halkin, M Singh, E Nikolsky, et al., *Prediction of Mortality After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction*, Journal of the American College of Cardiology, 45(9), 1397–1405. 2005; https://www.sciencedirect.com/science/article/pii/S0735109705004171?via%3Dihub

[15] DA Morrow, EM Antman, RP Giugliano, et al. *A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy*.;2006; https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(01)06649-1/fulltextA

[16] Kurtul, "*Usefulness of the CHA2DS2- VASc Score in Predicting In-Stent Restenosis Among Patients Undergoing Revascularization With Bare-Metal Stents", Clinical and Applied Thrombosis/Hemostasis,* https://journals.sagepub.com/doi/pdf/10.1177/1076029617716769

Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

--Etleva Beliu, and Endri Raço applied a range of statistical techniques, analyzed and interpreted statistical data, as well as formatted, and generated the reports of this scientific research.

-Kleida Haxhi, and Oriana Zaçaj planned and managed the complex databases.

Research Ethics and Consent

Participants were informed about the study and their consent was obtained. The study has complied with the rules and ethical codes specified in the Declaration of Helsinki.