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ADULT CARDIOLOGY

The Predictive Value of CHADS-VAS$_C$ Score in No-Reflow Phenomenon in Primary Percutaneous Coronary Intervention

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ABSTRACT

Objectives: To determine the role of CHADS-VASc Score in predicting No Reflow phenomenon in STEMI patients undergoing primary PCI.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: This study was carried out at a Tertiary Cardiac Care Center from Feb to May 2022.

Methodology: A total of (n = 320) patients who underwent PPCI at Armed Forces Institute of Cardiology from 4th February to 3rd May 2022 were enrolled in this study. Patients were divided into 2 groups, Comparision group with no NRP and NRP group. Descriptive statistics was run to present the categorical data in frequencies and percentages and continuous data in Mean±SD. Chi square test was applied to compare both groups regarding categorical and continuous variables. CHADS-VASc score was also compared in both groups.

Results: Out of (n=320) patients, 80(25%) patients developed NRP. Age, Diabetes, LV EF, history of stroke or TIA, peripheral arterial disease, TIMI thrombus grade, total stented length and CHADS-VASc score were found to be significantly associated with NRP. Binary logistic regression analysis revealed diabetes, LV EF, TIMI thrombus grade, total stented length and CHADSVaSc score to be independent predictors of NRP.ROC analysis revealed a cutoff CHADS-VaSc score of 3 to be a good predictor of NRP (sensitivity 65% and specificity 82%).

Conclusion: CHADS-VASc score can be an important pre-PCI tool to predict NRP during primary PCI.

Keywords: CHADS-VASc score, No-Reflow phenomena, Primary PCI.

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INTRODUCTION

Cardiovascular disorders are leading cause of death in the world. Traditionally, thought to be the inevitable outcome of industrialization and urbanization, these disorders have been on the rise in developing countries like Pakistan. According to International Institute of Health Metrics and evaluation, Pakistan observed a whopping 28.8% increase in deaths caused by cardiovascular disease.[1] The major burden of mortality is attributable to acute presentation of these disorders i.e., acute coronary syndrome /non-ST elevation Myocardial infarction (ACS/ NSTEMI) and ST elevation myocardial infarction (STEMI). STEMI is defined as symptoms of acute ischemia (chest pain or other atypical symptoms attributable to ischemia) and new ST-segment elevation in at least 2 contiguous leads of ≥0.2 mV in men or ≥0.15 mV in women in leads V2 to V3 and/or of ≥1 mm (0.1 mV) in other contiguous leads, or new left bundle branch block, later confirmed by increase in troponin. Temporal trends have shown increasing incidence of ACS/NSTEMI and falling trend in STEMI patients. Concomitantly the mortality rate of STEMI patients has significantly fallen over last two decades. Mortality in mid 90s was 16-18% and in mid of 2010s was 4%.[2] This improvement in early survival owes to the advent of Primary PCI as a treatment option for STEMI as evidenced firstly in PAMI study followed by 2003 meta-analysis by Keele *et al.*[3] Primary PCI is an emergent percutaneous catheter intervention in setting of STEMI without prior thrombolysis comprising of stenting of Infarct related artery.

The next logical goal in STEMI management is to further reduce early mortality rate and to decrease late mortality and morbidity. One of the important phenomena underlying poor acute PPCI outcomes and late poor myocardial healing and remodeling is No Reflow (NRP). First described by Ito in 1992 in Acute myocardial infarction patient it is essentially described as absence or sluggish epicardial coronary flow in the presence of patent stent (or other contemporary intervention), in absence of any other cause of mechanical obstruction and resulting in reduced perfusion of myocardium at tissue level. It is classified

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into,[4] groups according to severity. TIMI 0, no antegrade blood flow is present; TIMI I, antegrade flow is present but not completely filling the vessel; TIMI II, antegrade flow completely filling the vessel but not as briskly as non-infarct related artery; TIMI III, Brisk antegrade flow as good as non-infarct related artery. The estimated frequency of No Reflow is estimated from,[5] to 60% in different studies, a recent study from Tanjin Hospital China puts the incidence of NRP in Primary PCI at 29.5%.[6] Outcomes in patients with NRP is much worse than patients without NRP (32% VS 2.8%, p<0.0.001).[7]

The best strategy in treatment of NRP is prevention and the first step in prevention is to predict the patients' subgroups with higher risk of NRP which can result in avoidance (high pressure stent deployment and post dilation) or implementation (thrombus aspiration, GpIIbIIIA inhibitor infusion) of techniques to ameliorate NRP totally or partially. Many studies have looked into evaluating predictors of NRP which include both clinical and angiographic factors. Recently there has been a renewed interest in an old tool. Lip *et al.* refined classical CHADS score to CHADS-VASc score to include age modification, gender and arterial disease. This score has been consistently given Class-I recommendation for risk stratification of patients with Atrial fibrillation and to tailor anti thrombotic therapy accordingly. The CHA2DS2-VASc score is calculated as follows: 1 point each is assigned for recent congestive heart failure, a history of hypertension, a history of diabetes mellitus, age 65 to 74years, vascular disease and sex category (women). Two points are assigned for a history of stroke or transient ischemia attack and age ≥75 years. Recent studies have shown the effectiveness of this score in predicting NRP in patients undergoing primary PCI, though no such study has been performed nationally. The rationale of this study is to evaluating the effectiveness of CHADS VASc score in predicting NRP which can identify high risk patient population with timely implementation of peri-procedural interventions to prevent NRP.[8]

Our study was aimed to determine the role of CHADS-VASc Score in predicting No Reflow phenomenon in STEMI patients undergoing primary PCI.

METHODOLOGY

This study was descriptive cross-sectional study carried out at a Tertiary Cardiac Care Center from Feb 2022 to May 2022.

Sample Size: n=320 was computed using WHO calculator at confidence level of 95% and Precision 5% keeping the prevalence of No Reflow in STEMI patients treated with primary PCI as 29.5%.[6] Non-probability, consecutive sampling technique was used to collect data.

Inclusion criteria: Both male and female patients above the age of 20 years presenting with STEMI and undergoing primary PCI were included in the study. **Exclusion criteria:** Patients with recent administration of thrombolytic agent i.e., Rescue PCI, patients having contraindication for coronary angiography, patients having valvular heart disease or non-ischemic dilated cardiomyopathy, or myocardial infarction with non-obstructive coronary artery disease (MINOCA) or with previous history of CABG were excluded from this study.

After approval from IERB (IERB letter # 9/2/R&D/2022/166), a total of 320 patients undergoing Primary were enrolled in this study after attainment of informed consent. CHADS-VASc score was calculated before PPCI. Primary PCI was carried out as per protocol with the target door to device time of less than 90 minutes. TIMI flow was assessed post stenting and/or Post dilation. Patients developing TIMI flow <III post stenting or post dilation were labelled as having No Reflow Phenomena. All the relevant information was documented on a preformed proforma. Patients were divided into two groups i.e., with NRP and without NRP CHADS-VASc score both groups was compared.

All statistical tests were conducted using the Statistical Package for the Social Sciences 25 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD or median (interquartile range), and categorical variables were expressed as frequencies and percentages. The Chi-square test was used to assess differences in categorical variables between groups. ANOVA test was used to compare continuous variables in control and NRP group. The variables with significant association were put into Multivariate logistic regression analyses and thus independent predictors of no-reflow were determined. The results of univariate and multivariate regression analyses were presented as odds ratio (OR), with 95% confidence intervals (CI). All statistical tests were two-tailed, and a p-value of <0.05 was considered as statistically significant. Receiver operating curve (ROC) analysis was done to check validation of CHADS-VASc score.

RESULTS

A total of (n=320) patients undergoing primary PCI were involved in this study. Mean age of patients

was 60 years. Most of the patients who came with STEMI were middle aged (50.5%) or elderly (45.5%). Only a handful of patients were aged below 40. There was clear dominance of male patients (n=277; 86.56%). Regarding risk factor profile, hypertension was most prevalent risk factor 100(41.7%) in non-NRP group while diabetes (n=56; 70.0%) was in NRP group. The Nearly all of the patients underwent Pre dilation 230(95.3%). Multiple stents were used in 19(7.9%) & 18(22.5%) in Comparision and NRP groups respectively and post dilation with non-compliant balloon was done in 226(94.2%) of cases. Out of (n=320) patients (n=80) had NRP (25%) i.e., one fourth of the cohort. Most of the patients had mild NRP with

Table-I: Demographics and Clinical Findings

Characteristics		**Comparision group (n=240) n (%)**	**NRP (n=80) n(%)**	***p*-value**
Age in years (Mean±SD)		59.06±11.14	64.16± 11.44	<0.01
Gender **n(%)**	Male	208(86.7%)	69(86.2%)	0.925
	Female	32(13.3%)	11(13.8%)	
Comorbids n(%) (Mean±SD)	Diabetes	74(30%)	56(70%)	<0.01
	Hypertension	100(41.7%)	41(51.2%)	0.135
	Smoking	58(24.2%)	15(18.8%)	0.317
	Family History of IHD	31(12.9%)	7(8.8%)	0.318
	Dyslipidemia	29(12.1%)	7(8.8%)	0.414
	Stroke/TIA	2(0.8%)	5(6.3%)	0.004
	Arterial Disease	3(1.25%)	8(10%)	<0.01
	LV EF%	43.8±6.84	37.75±5.27	<0.01
Clinical Findings				
CHADSVASc Score **(Mean±SD)**		1.68 ±1.18	3.02±1.20	<0.01
Anterior STEMI		123(51.2%)	45(56.2%)	0.194
Inferior STEMI		88(36.7%)	31(38.8%)	
Lateral STEMI		29(12.1%)	4(5%)	
IRA LAD		123(51.2%)	45(56.3%)	0.319
IRA RCA		76(31.7%)	29(36.3%)	
IRA LCX		38(15.8%)	6(7.5%)	
TIMI Flow grade (Mean±SD)		1.27 ±1.38	1.02±1.32	0.158
TIMI thrombus grade (Mean±SD)		2 ±1.67	5±1.24	<0.01
Pre-Dilation		230(95%)	76(95%)	0.7
Total stented length (Mean±SD)		30.8 ±12.93	39.9 ±17.88	<0.01
IRA= Infarct related artery				
Multiple stents		19(7.9%)	18(22.5%)	<0.01
Post Dilatation		226(94.2%)	67(83.8%)	0.004

mean CHADS-VASc score of the cohort was 3.02±1.2 in NRP group while in Comparison group it was 1.68±1.18. Regarding MI, Anterior wall MI was most common 123(51.2%) followed by Inferior wall MI 88(36.7%) and Lateral wall STEMI 29(12.1). The most common Infarct Related artery (IRA) was LAD 123(51.2%). Most frequent non-Infarct related artery was LCX (21.9%), followed by LAD (20.2%), RCA (14.3%) and LMS (1.9%). Adhoc PCI of NIRA was attempted only in 5.9% of cases.

Regarding procedural characteristics, totally occluded vessels were seen in 53.6% of cases while TIMI flow-I, II and III were seen in 2.8%, 11.8% and 31.5% of cases respectively. High thrombus burden i.e., TIMI thrombus Grade-III, IV and V was seen in 43 (13.4%), 23(7.2%) and 116(36.4%) of cases respectively. TIMI-II flow in 16.9% and more severe NRP in rest of the cases i.e., TIMI flow-0 in 1.3% and TIMI flow-I in 7.2%. After appropriate management TIMI flow-III was secured in 95.6% of cases, while only 0.9% of patients had final TIMI flow less than-II (Table-I).

For analytical purpose, cohort was divided into Comparison group i.e., without NRP and No Reflow phenomena group. Comparative analysis (Table-I) between these groups showed that age was significantly associated with NRP, with patients in NRP group significantly older (median age in NRP 63.5y vs 59y in control $p<0.001$). Gender was not a significant factor in determining NRP ($p>0.05$). Among risk factors and co morbidities, diabetes, stroke or TIA and Arterial disease were significantly associated with NRP. Mean Ejection fraction (EF) was significantly

lower in NRP group i.e. 37.75±5.27 as compared to Comparison group 43.8±6.84 (p<0.01). Eta measure of association was 0.379 for EF. CHADS-VASc score was significantly higher in NRP group (mean score 3.02) vs control group (mean score 1.68) with p<0.01 and eta measure of association 0.440. Territory of STEMI or IRA was not associated with NRP.

Regarding procedural characteristics, TIMI thrombus grade was significantly worse in NRP group i.e. median grade 5 vs control group i.e. 2 (p<0.01). Pre PCI TIMI flow grade was not a significant factor in determining NRP. Total stented length was significantly higher (p<0.01) in NRP group (mean length 39.9mm and median 38mm) vs control group (mean 30.6mm and median 28mm). Use of multiple stents was also significantly associated with NRP. Use of post dilation was also compared in two groups and the use of NC was significantly lower in NRP group which may well be a biased finding in this non randomized study.

The variables having significant association with NRP were put into logistic regression analysis, results of which are shown in Table-II. Logistic regression analysis (Table-II) shows that diabetes, LV EF, CHADS-VASc score, Thrombus grade and stented length were significant independent predictors of NRP. Increase in CHADS-VASc score by one unit increased the likelihood of NRP by 1.55 times (95% CI (1.02-2.22) p<0.01). Age was not found to be an independent predictor of NRP.

Table-II: Predictors of NRP

Parameter	B	*p*-value	Exp(B)
Age	0.024	0.186	1.024
Diabetes	1.313	0.000	0.269
Stroke or TIA	0.890	0.411	2.434
LV Ejection Fraction	-0.129	0.000	0.879
Arterial Disease	0.460	0.676	0.632
CHADSVaSc Score	0.441	0.015	1.555
Thrombus Grade	0.455	0.000	1.576
Total Stent Length	0.032	0.004	1.033
Constant	-0.890	0.687	0.411

The ROC analysis was conducted on CHADS-VASc score. Results are shown in the Figure. These analyses reveal that a score of 3 or more has sensitivity of 65% and specificity of 82% while a score of 2 or less gives a sensitivity of 92% and specificity of 43% in predicting NRP (Area under the curve 0.794, 95% CI lower 0.74 and 95% CI upper 0.84).

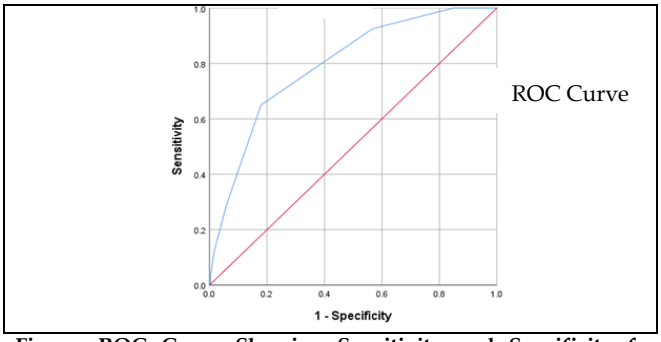

Figure: ROC Curve Showing Sensitivity and Specificity for Different Grades of CHADS-VASc Score

DISCUSSION

No Reflow Phenomena is the most common complication of primary PCI with negative impact on both short term and long-term clinical outcomes. No Reflow presents as slow flow after mechanical opening of epicardial vessel and is diagnosed as cause of slow flow after exclusion of mechanical causes like dissection, air embolism etc. It occurs due to microvascular dysfunction at the level of microvasculature and impairs distal myocardial blood and O^2 delivery even in presence of open epicardial vessel. Genetic preponderance, ischemic injury, reperfusion injury and micro emboli have all been postulated as the causative mechanism for this dreaded complication.[9]

In our study NRP occurred in every fourth patient i.e., 25% incidence. Different studies have put the incidence of NRP from 5-50%.[10] This variability is explainable by different demographics, genetic makeup of population and differing peri-procedural care during primary pci over last 2 decades. In the recent NORM PPCI trial conducted by Rossington *et al.* in UK placed the incidence of NRP at 13.9%.[4] The incidence is relatively higher in subcontinent with a recent study from India by Sabin et al estimating the incidence of NRP at 25.9%.[11] A study closer to home in from Karachi found the incidence of NRP at 32.9%.[12] These studies demonstrate the common occurrence of NRP during PPCI and emphasize the need to predict and counter this complication.

In this study, CHADS-VASc score, Diabetes, LV ejection fraction, TIMI thrombus grade and total stented length were found to be independent predictors of NRP in logistic regression analysis. In pioneering study by Ndrepepa *et al.* published in JACC, 10 variables were found to be predictors of NRP i.e., elderly, smoking history, Acute myocardial infarction, heart failure, serum creatinine, C-reactive protein, time since symptom onset, LVEF, baseline TIMI flow, & initial scar size.[13]

The utility of CHADS-VASc score in predicting is established in this study with patient having NRP having significantly higher score (mean 3.02 vs 1.68 p<0.01). Multivariate Regression analysis showed odds ratio of CHADS-VASc in predicting NRP to be 1.55(95% CI 1.02-2.22 p<0.01). ROC analysis showed a cutoff score of 3 or more gives a sensitivity of 65% and specificity of 82% in predicting NRP. In a Turkish study by Zorlu *et al.* showed CHADS-VASc score to be significant independent predictor of NRP (OR: 1.56, 95% CI: 1.31–1.84; p<0.001).[14] They used a cut off of 2 or more in predicting NRP which gave sensitivity of 66% and specificity of 54%. Our study shows that a cut off value of 3 can provide a more robust parameter predicting NRP. Another Turkish study by Barman et al, using a CHADS-VASc score cutoff value of 3, showed sensitivity of 80.9% and specificity of 74.6% in predicting NRP. These findings are quite similar to our study. In a Chinese study, Huan *et al*,[16] found that the incidence of NRP in patients with CHA2DS2-VASc score ≥3 was 1.7 times higher than that in patients with CHA2DS2-VASc score <315.

Apart from CHADS-VASc score, TIMI thrombus grade, total stented length and LV ejection fraction are also independent predictors of NRP. As embolism of thrombus is one of the main mechanisms of NRP, the association of heavy thrombus burden with NRP is quite understandable (OR 1.57 95% CI 1.25-1.98, p<0.1). Similar findings were noted in a Brazilian study linking heavy thrombus burden with NRP (OR 1.[17]

This study reinforces the use of CHADS-VASc score as a simple and rapid bedside tool in predicting NRP during PPCI. Other risk scoring systems used in STEMI patients like TIMI score give insight into clinical outcomes but do not predict NRP.[17] CHADS-VASc score can be used in addition to these clinical risk scores to predict the occurrence of NRP and to employ preventive strategies in advance to improve clinical outcomes.

A score of 3 or more predicts high risk of NRP and preventive strategies like balloon-less stenting, focal stenting and use of GPIIbIIIa inhibitors can be employed in this cohort. Though a study will be required to evaluate whether such preventive strategies in high-risk patients can improve clinical outcome or not. Though other studies have proven the efficacy of CHADS-VASc score in predicting in hospital mortality for STEMI patients in addition to foreseeing NRP during PPCI.[18,19]

LIMITATIONS OF STUDY

This study was a single center study so the sample size was quite small and the generalizability of results is quite limited. Secondly this study fails to document the clinical impact of calculation of CHADS-VASc score routinely during PPCI. Data regarding in hospital or long-term outcomes were not collected and evaluated in this study.

CONCLUSION

CHADS-VaSc score can be thought of as a combination of pro thrombotic risk factors. As thromboembolism forms the basis of NRP, the role of CHADS-VASc score in prediction of NRP is quite unsurprising. This study provides ample evidence for a new application of CHADS-VASc score i.e., in prediction of NRP during primary PCI.

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Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AF: Manuscript writing, Data collection, analysis discussion

NAS: Intellectual contribution, concept and final approval

AA: Study design, drafting the manuscript & critical review

HMS: Data collection, data analysis and review of article

MNT: Drafting the manuscript, proof reading & critical review

SS: Data analysis, manuscript writing and proof reading

NA: Drafting the manuscript, proof reading & critical review

JK: Manuscript writing, Proof reading, final approval

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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