



Association of Neutrophil to Lymphocyte Ratio as a Predictor of New Onset of Atrial Fibrillation After Off Pump Coronary Artery Bypass Grafting

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Abstract

Background: Atrial fibrillation is frequently seen in patients underwent off pump coronary artery bypass graft. Neutrophilia and lymphopenia may be strongly associated with developing atrial fibrillation by both electrical and structural remodeling of the atrium due to atrial fibrosis and oxidative stress also plays an important pathological role. The aim of this study is to investigate the association of neutrophil to lymphocyte ratio with postoperative atrial fibrillation in the patients who underwent off pump coronary artery bypass grafting.

Methods: This comparative cross sectional study was carried out in department of cardiac surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka. Total 70 patients were selected for this study, divided into two groups. Among them, 35 patients with preoperative neutrophil to lymphocyte ratio level ≥ 2.63 were in group A and 35 patients with preoperative neutrophil to lymphocyte ratio level < 2.63 were in group B. The data was collected by semi structured questionnaire and reviewing medical records. The continuous data was evaluated by independent t-test and categorical data by chi-square test, where quantitative as mean & SD and qualitative as frequency & percentage. Prediction was reviewed using logistic regression analysis. P value ≤ 0.05 was significant for data analysis which was summarized in tables & charts. Ethical approval was taken from the institutional review board of Bangabandhu Sheikh Mujib Medical University.

Results: The Mean \pm SD age was 52.71 ± 11.49 in group A and 51.91 ± 10.04 in group B. There were 28 (80%) male in group A and 34 (97.1%) male in group B and also 31 (88.6%) patients in group A had hypertension where as 24 (68.6%) patients in group B had hypertension which was statistically significant. Postoperative atrial fibrillation occurred in 28 (80%) of patients in group A whereas only 2 (5.7%) patients in group B which was statistically significant. In the logistic regression model, Neutrophil to lymphocyte ratio was found to be an independent predictor for new onset of postoperative atrial fibrillation development with 70% sensitivity, 87.5% specificity, OR 5.649, 95% CI 2.353 – 13.562, $p=0.001^S$.

Conclusion: This study showed that there is association between the preoperative neutrophil to lymphocyte ratio as a predictor of new onset of postoperative atrial fibrillation after off-pump coronary artery bypass graft.

Abbreviation

ABG	=	Arterial Blood Gas
AF	=	Atrial Fibrillation
AHA	=	American Heart Association
AKI	=	Acute Kidney Injury
ASA	=	American Society of Anaesthesiologist
AUC	=	Area Under the Curve
BMI	=	Body Mass Index
BP	=	Blood Pressure
BSMMU	=	Bangabandhu Sheikh Mujib Medical University
CABG	=	Coronary Artery Bypass Graft
CAD	=	Coronary Artery Disease
CAG	=	Coronary Artery Angiogram
CI	=	Confidence Interval
CKD	=	Chronic Kidney Disease
CMV	=	Controlled Mandatory Ventilation
COPD	=	Chronic Obstructive Pulmonary Disease
CPB	=	Cardio Pulmonary Bypass
CRP	=	C - Reactive Protein
CVTS	=	Cardiovascular and Thoracic Surgery
DALYs	=	Disability – Adjusted Life Years
DM	=	Diabetes Mellitus
DVD	=	Double Vessels Diseases
ECG	=	Electrocardiogram

EDTA =	Ethylenediamine Tetraacetic Acid
GBD =	Global Burden of Cardiovascular disease
GSV =	Great Saphenous Vein
HDU =	High Dependency Unit
ICU =	Intensive Care Unit
IHD =	Ischemic Heart Disease
IRB =	Institutional Review Board
LA =	Left Atrium
LAD =	Left Anterior Descending
LCX =	Left Circumflex
LIMA =	Left Internal Mammary Artery
LMD =	Left Main Disease
LVEF =	Left Ventricular Ejection Fraction
MI =	Myocardial Infraction
MPO =	Myeloperoxidase
NADPH=	Nicotinamide Adenine Dinucleotide Phosphate
NLR =	Neutrophil to Lymphocyte Ratio
NYHA=	Newyork Heart Association
OPCAB=	Off-Pump Coronary Artery Bypass Graft
OR =	Odds Ratio
PLR =	Platelet Lymphocyte Ratio
PoAF =	Post-Operative Atrial Fibrillation
POD =	Postoperative Day
SD =	Standard Deviation

SVD = Single Vessel Disease

TVD = Triple Vessels Disease

WBC = White Blood Cell

Introduction

Coronary artery bypass graft surgery is the definite surgical procedure for the treatment of ischemic heart diseases. CABG resolves symptoms and improves the survival of the patients suffering from severe coronary artery diseases (Roger et al. 2012). Conventional CABG is performed on cardiopulmonary bypass (CPB) which have some serious complications like stroke, kidney or liver failure, decrease in higher mental function and bleeding (Shekar P et al. 2006). Off-pump coronary artery bypass graft (OPCABG) operation possibly avoid the risk of extracorporeal circulation although there are some possible risks which include infection, bleeding, atrial fibrillation, blood clots leading to stroke or heart attack, kidney failure and complications from anesthesia among which postoperative atrial fibrillations is greater distress for the cardiac surgeons. Therefore, it is very much necessary to rule out patients at risk and take effective prophylaxis and management on due time to reduce the associated risks of adverse outcome.

Neutrophil to lymphocyte ratio (NLR) has emerged as a novel systemic inflammatory marker and also as a prognostic indicator of adverse cardiovascular complications (Papa A et al. 2008). Neutrophil are activated non-specific inflammatory cell which are attracted to the myocardium during & after cardioplegia and CPB by a diffuse failure of endothelial cells, later resulting from ischemia and reperfusion injury (Jacob KA et al. 2014). Lymphopenia is a marker of physiological stress. Both raised neutrophil and lymphopenia are indicators of inflammation and inflammation can alter conduction, facilitating re-entry thus predispose the development of postoperative atrial fibrillation (Echahidi N et al. 2008). NLR seems significantly higher in the CPB group compared with the OPCAB group (Aldemir M et al. 2015).

Neutrophilia represent activated non-specific inflammation and lymphopenia is a marker of poor general health and physiological stress. NLR shows the balance between the neutrophil and lymphocyte levels and integrates these two important and opposite immune pathways which serve as a measures of both systemic inflammation and stress response (Shao Q et al. 2015). Leukocytes were identified in atrial tissue of AF patient's even without an underlying structural heart disease (Frustaci

A et al. 1997). Inflammation appears to be a critical confounder for structural remodeling of the atria and thus for genesis of atrial fibrillation (Spodick DH, 1997).

Neutrophils are major constituents of the innate immune system. Local endothelium release local cytokines and expression adhesion molecule that attracts neutrophils due to expression of integrins (CD11b/ CD18) on the leukocytes outer membrane which is the principal pre requisite for the leukocytes subsequent extravasations. Neutrophils release myeloperoxidase (MPO) and matrix metalloproteinase (MMP) stored in primary granules of neutrophils, to endothelial cells via -a direct CD11b/ CD18 –integrins mediated intercellular link. These enzymes known to accelerate tissue remodeling and atrial fibrosis by increasing deposition of interstitial matrix such as collagen I & II and fibronectine which impairs atrial conduction, allowing for an increased electrical ectopic and re-entry. Thus atrial fibrosis plays a major role in the pathogenesis of atrial fibrillation (Friedrichs K et al. 2014).

Postoperative atrial fibrillation is the commonest arrhythmia observed in 18-40% of patients after isolated coronary artery bypass surgery (El-Chami 2010; Ozturk 2019), 35-40% after isolated valvular surgeries and even higher from 35% to greater than 60% after combined coronary artery bypass graft (CABG) and valve surgery (Greenberg J et al. 2017) which may leads to hemodynamic disturbances associated with increased risk of embolism, heart failure, prolong hospital stay and increase cost.

Postoperative atrial fibrillation onset follows nonlinear trend and usually highest on 2nd postoperative day. Onset depends on risk factors and can be divided into two phases of risk. First phase of risk occurs immediately after surgery and declines sharply during first 18 hrs depending upon factors like elderly age, prolong cross clamp time and mitral valve surgery. The second phase increase to a peak from hour zero to 36-48 hrs depending upon the risk factors like advanced age, greater weight, Caucasian race and mitral valve surgery (Greenberg J et al. 2017).

Postoperative atrial fibrillation was found as a major morbid event (Almassi et al. 2007), which is associated with thromboembolism and stroke (Fuller et al. 2007), ventricular dysrhythmias, hemodynamic instability (Aranki et al. 2006), and iatrogenic complication associated with therapeutic interventions. AF results ineffective irregular contraction and incomplete ejection of blood, especially within the left atrial appendage which is the main source of thrombus formation in patients with AF (Safavi-Naeini et al. 2020). There is about 3-fold greater risk of perioperative stroke for the patients with postoperative atrial fibrillation. About 3,855 patients went cardiac surgery among which hospital mortality and 6-month mortality were significantly more in patient with postoperative atrial fibrillation (Almassi et al. 2007).

The etiology of postoperative atrial fibrillation after OPCABG are most likely multifactorial which include metabolic abnormalities (hyperuricemia, hypoxia, hypothyroidism, diabetes), advanced age, male sex, hypertension, withdrawal of β -blockers, impaired cardiac function, chronic renal failure, myocardial ischemia and reperfusion, myocardial infarction, right coronary artery disease, excessive catecholamine, electrolyte imbalance, particularly hypomagnesemia, (Kohno et al. 2005) as well as inflammatory and oxidative changes which closely linked to initiation of atrial fibrosis and AF. The inflammatory mediators contribute to postoperative atrial fibrillation has been suggested by evidence of high C-reactive protein (CRP) and white blood cell (WBC) count within 3 days after cardiac surgery (Walsh J et al. 2017).

For these reasons, inflammatory parameters have been the subject of research to rule out the results after cardiac surgery, just as in many areas of medicine, and exert various effects on cardiovascular diseases. It also has been reported that preoperative calculated NLR may be associated with postoperative atrial fibrillation (Gibson PH et al. 2007).

In BSMMU, no study has yet been carried out for the prediction of postoperative atrial fibrillation by using NLR. Therefore in this study we aim to investigate whether NLR can be used preoperatively as an early predictor of postoperative atrial fibrillation after off – pump coronary artery bypass graft.

Rationale of the Study

Postoperative atrial fibrillation is a common complication after off-pump coronary artery bypass graft which leads to thromboembolism, stroke, ventricular dysrhythmia, hemodynamic compromise and many more, and directly linked to inflammatory process which leads to atrial fibrosis. Complete blood counts routinely done for all the patients as preoperative investigations during optimization of the patients. Neutrophil to lymphocyte ratio, a novel and inexpensive biomarker, is reported to physicians in clinical practice as part of the automated complete blood count. However, Neutrophil to lymphocyte ratio is usually overlooked while studying simple complete blood count report.

Previous meta-analysis and prospective studies have shown that higher Neutrophil to lymphocyte ratio is associated with postoperative atrial fibrillation in patients undergoing isolated off-pump coronary artery bypass graft. Although there are many risks assessment methods which are used to assess risk but even have some limitations. The risk assessment tools need improvement to know which patients should be closely monitored for atrial fibrillation after surgery. So, new tool need to be established which ought to be simple enough for clinical use and cost-effectiveness. Hence, Neutrophil to

lymphocyte ratio can be utilized to upgrade risk models which further benefit the surgical patients without extra financial burden.

Recently, some studies have shown the predictive role of Neutrophil to lymphocyte ratio in postoperative atrial fibrillation. However, previously, no studies have been carried out in Bangladesh to see the predictive role of Neutrophil to lymphocyte ratio for postoperative atrial fibrillation after off-pump coronary artery bypass graft. The study was attempted to establish the predictive role of Neutrophil to lymphocyte ratio for atrial fibrillation after off-pump coronary artery bypass graft that would be helpful for further management of patients.

Research Hypothesis

Preoperative neutrophil to lymphocyte ratio has an association as a predictor of new onset of atrial fibrillation in the patient following off-pump coronary artery bypass graft.

Objectives of the Study

General Objective

- To evaluate the association between preoperative neutrophil to lymphocyte ratio and postoperative atrial fibrillation after off-pump coronary artery bypass graft.

Specific Objectives

- To obtain the NLR of the patients in both groups.
- To compare the incidence of AF in early postoperative period between the groups.
- To establish the predictive value of preoperative NLR level for prediction of the postoperative AF after OPCAB.
- To assess the effect of NLR on postoperative ventilator support, duration of ICU stay and postoperative morbidity or mortality due to thromboembolism.

List of Variables:

Dependent Variable:

New onset of atrial fibrillation

- By continuous ECG monitoring

Independent Variable:

- Preoperative neutrophil to lymphocyte ratio

Confounding Variables:

Variables related to demographic and anthropometric characteristic:

- Age
- Sex
- Body Mass Index (BMI)

Variables related to risk factors:

- Hypertension
- Hyperlipidemia
- Diabetes mellitus
- Smoking

Variables related to preoperative laboratory findings:

- Serum creatinine
- Serum electrolytes - sodium and potassium
- Echocardiography findings – left atrial diameter, left ventricular ejection fraction (%)

Variables related to per operative attributes:

- Duration of Surgery
- Total number of bypass grafts

- Per operative Atrial fibrillation

Variables related to postoperative attributes:

- Duration of mechanical ventilator support
- Duration of ICU and hospital stay
- Arterial Blood Gas (ABG) analysis
- Postoperative serum creatinine and magnesium
- Duration of Postoperative Inotropic support
- Mortality and Morbidity due to thromboembolism

Operational Definitions

Arrhythmia:

A cardiac arrhythmia is a disturbance of the electrical rhythm of the heart. Arrhythmias are often a manifestation of structural heart disease but may also occur because of abnormal conduction or depolarization in an otherwise healthy heart (Davidson, 2014. pp.562).

Atrial Fibrillation:

AF is a complex arrhythmia characterized by both abnormal automatic firing and the presence of multiple interacting re-entry circuits looping around the atria. Episodes of atrial fibrillation are initiated by rapid bursts of ectopic beats arising from conducting tissue in the pulmonary veins or from diseased atrial tissue. AF becomes sustained because of re-entrant conduction within the atria or sometimes because of continuous ectopic firing (Davidson, 2014. pp. 564).

New onset AF:

A patient with new symptom attributable to AF or an asymptomatic patient with irregularly irregular and rapid impulse is known as new onset AF.

Neutrophil to lymphocyte ratio:

The NLR is simply the number of neutrophils divided by the number of lymphocytes. Under physiologic stress and inflammation, the number of neutrophils increases, while the number of lymphocytes decreases. The NLR combines both of these changes, making it more sensitive than either alone.

$$NLR = \frac{\text{relative \% neutrophils}}{\text{relative \% lymphocyte}}$$

Interpretation: depends on clinical context. However, to provide some idea of how to interpret this:

- A normal NLR is roughly 1-3.
- An NLR of 6-9 suggests mild stress.
- An NLR of 9-18 suggest moderate stress.
- An NLR > 18 suggest severe stress.

Body mass index:

It was calculated by the following method:

$$BMI = (\text{weight in kg}) / (\text{height in meter})^2$$

Ejection fraction:

Left Ventricular Ejection fraction is a measurement percentage of blood the left ventricle pumps out with each cardiac cycle. It is calculated as the difference between LV end-diastolic volume (EDV) and end-systolic volume (ESV) divided by LV end-diastolic volume (EDV).

LVEF = stroke volume (EDV - ESV) ÷ EDV It remains the most commonly used method for assessing systolic function.

Acidosis:

Increase H⁺ concentration with decrease pH below 7.35 (Ralston, 2018, p. 363).

Alkalosis:

Decrease H⁺ concentration with increase pH above 7.45 (Ralston, 2018, p. 363).

Normal renal function:

Those patients who had serum creatinine level < 1.4mg/dl (Shilpak, et al. 2002).

NYHA:

The Newyork Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and/or angina pain.

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and /or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bed bound patients.

Methods

Study design:

This study was a Comparative Cross- Sectional study.

Study Population:

Patients admitted to the department of cardiac surgery, BSMMU who underwent off pump coronary artery bypass grafting surgery.

Place of study:

Citation: Dr. Bijay Kumar Sah, "Association of Neutrophil to Lymphocyte Ratio as a Predictor of New Onset of Atrial Fibrillation After Off Pump Coronary Artery Bypass Grafting" MAR Cardiology Volume 5 Issue 3
www.medicalandresearch.com (pg. 12)

The study was conducted at Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka - 1000, Bangladesh which is a 60 bedded well equipped tertiary level hospital with thoracic and vascular wings providing multidisciplinary support and advanced technologies for surgical care of cardiac patients.

Period of study:

The study was conducted within the period of 24 months commencing from September 2020 to August 2022. During this time, protocol development, protocol submission, literature review, research instrument development, data collection, data entry, processing and analysis was done.

Grouping of patients:

Cut off value for NLR was 2.63 (Gibson PH, et al., 2010).

- Group A = 35 patients who had preoperative neutrophil to lymphocyte ratio ≥ 2.63 .
- Group B = 35 patients who had preoperative neutrophil to lymphocyte ratio < 2.63 .

Sample Size:

- Sample size was total 70 (in each group 35).

Formula to calculate sample size

We hypothesized the NLR at cutoff point 2.63 should detect the patients with atrial fibrillation after off pump CABG with a specificity of 80% or greater. The sample size will be calculated for a power level of greater than 80%, an α error of 0.05, and an expected specificity of 68% or greater based on previous reports (Gibson PH, et al., 2010).

Solution:

Citation: Dr. Bijay Kumar Sah, "Association of Neutrophil to Lymphocyte Ratio as a Predictor of New Onset of Atrial Fibrillation After Off Pump Coronary Artery Bypass Grafting" MAR Cardiology Volume 5 Issue 3
www.medicalandresearch.com (pg. 13)

It is assumed that both the diagnostic test and the criterion standard are dichotomous tests. That is, a subject either tests positive or negative; a subject either has the expected outcome (≥ 2.63 cutoff point) or no expected outcome (no or <2.63).

Sample size calculation based on specificity (Buderer's formula):

$$\frac{Z_{1-\frac{\alpha}{2}}^2 \times S_p \times (1 - S_p)}{L^2 \times (1 - Prevalence)}$$

Sample size (n) based on specificity = The ingredients for the sample size calculation are as follows:

n = required sample size Sp= anticipated sensitivity

α = size of the critical region (1- α is the confidence level)

Z $_{1-\alpha/2}$ = standard normal deviate corresponding to the specified size of the critical region (α)

L= absolute precision desired on either side (half-width of the confidence interval) of specificity P= the estimated prevalence of disease in the target population (patients who have clinically Suspected coronary artery disease) Sp=80%

α = 5%

Z $_{1-\alpha/2}$ = 1.96

L = 10%

Prevalence = 5% (in our hospital setting 5% patients could have coronary artery disease)

$$\text{So, } n = \frac{1.96^2 \times 0.8 \times (1 - 0.8)}{0.1^2 \times (1 - 0.05)}$$

= 64.67

According to the formula mentioned above, my sample size will be 70 which will be divided in two group each having 35 number of patients.

Sampling method:

Convenience sampling method was applied for this study.

Selection criteria of patients:

Citation: Dr. Bijay Kumar Sah, "Association of Neutrophil to Lymphocyte Ratio as a Predictor of New Onset of Atrial Fibrillation After Off Pump Coronary Artery Bypass Grafting" MAR Cardiology Volume 5 Issue 3
www.medicalandresearch.com (pg. 14)

Participants enrolled in this study that underwent OPCAB with fulfilling inclusion and exclusion criteria.

Inclusion criteria:

- Patients admitted in the department of cardiac surgery in BSMMU for Off Pump Coronary Artery Bypass Graft and willing to participate in the study.

Exclusion criteria:

1. Patients had been treated for AF by anti-arrhythmic drugs
2. Impaired renal function
3. Patients with hepatic disease
4. OPCAB converted to on pump CABG
5. Associated acute or chronic lung diseases
6. Patients with any electrolytes abnormality
7. Re-do surgery
8. Emergency surgery

Study procedure:

All relevant data was collected from each respondent by use of interview schedule, measured parameters and investigations in a predesigned format.

- All patients admitted in the department of cardiac surgery, BSMMU, Dhaka, scheduled for Off Pump CABG fulfilling the inclusion and exclusion criteria was considered for enrollment in this study.
- Informed written consent was taken from each patient before enrollment.
- Meticulous history was taken and detailed clinical examination was performed and recorded in predesigned structured data sheet.
- Demographic and anthropometric data such as age, sex & bmi was recorded.
- Preoperative complete blood count was measured using SYSMEX 6-Part Diff. Automated Hematology Analyzer at biochemistry laboratory, BSMMU.
- With all aseptic precaution, about 3 ml of whole was collected preoperatively by venipuncture of the patient and immediately transferred in EDTA tube containing EDTA potassium salt

additive as an anticoagulant. Tube was labeled with patients name, ID number & collection date and sent to BSMMU Biochemistry laboratory immediately for measurement of complete blood count.

- NLR level calculated manually by calculator.
- Patients were divided into two groups on the basis of preoperative neutrophil to lymphocyte ratio (NLR) level:-
Group A: NLR level ≥ 2.63
Group B: NLR level < 2.63
- All routine investigations including echocardiogram were performed.
- A standard anesthetic protocol was used throughout the study.
- All the patients were undergone median sternotomy and standard Off Pump CABG was performed.
- During the procedure systolic BP was kept $>80\text{mmHg}$.
- Postoperatively patient was shifted to ICU then to HDU/step-down then to ward.

Monitoring of:

- Arterial Blood Gas (ABG) & electrolytes – daily for 5 days by TechnoMedica GASTAT-603IE blood gas system auto analyzer.
- PoAF was assessed by continuous ECG monitoring for day 5.
- Serum creatinine and magnesium levels, daily for 3 days by Siemens Automated biochemistry Analyzer Dimension EXL with LM, USA.

The impact of different variables on either group was evaluated accordingly.

Data collection form was filled and collected throughout my study period and was accumulated at the end of the study period.

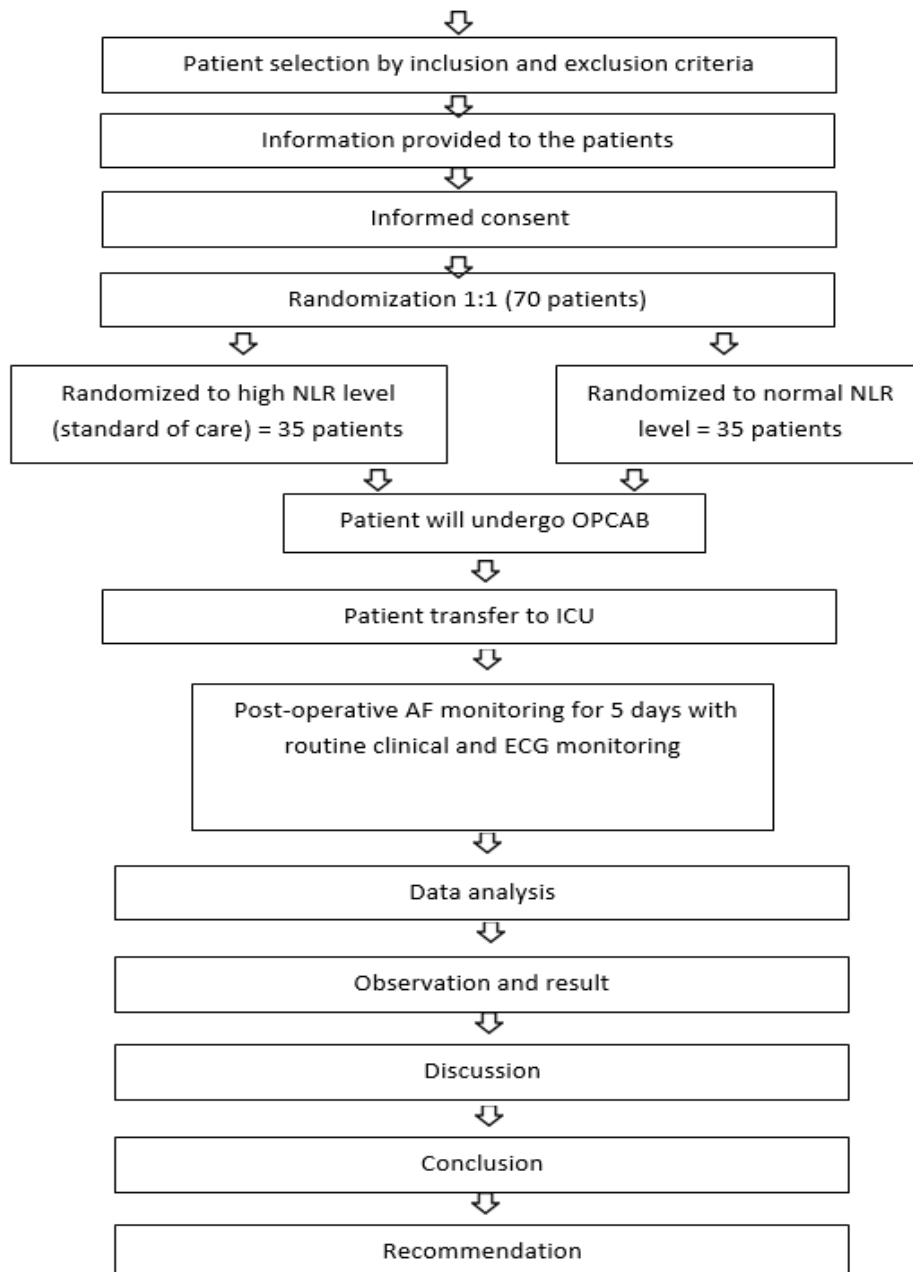
Anaesthesia & Surgical technique

All patients received a standard general anesthesia protocol for surgery through a standard median sternotomy approach. OPCAB performed by using left internal mammary artery and reversed saphenous vein graft as a conduit.

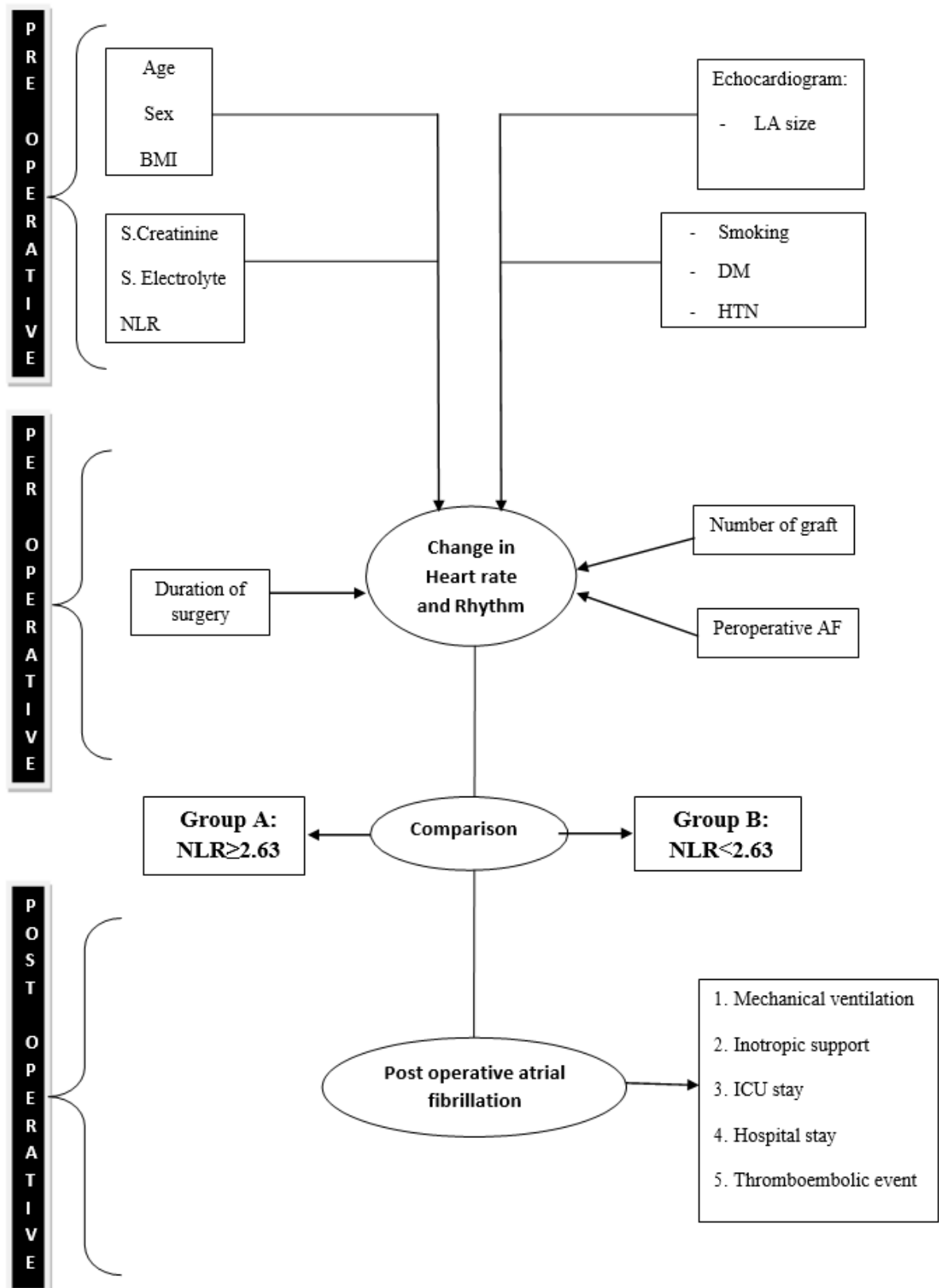
Postoperative evaluation

At the end of the surgery, the patients were transferred to the Intensive Care Unit (ICU). Initially, they will be ventilated with controlled mandatory ventilation (CMV) followed by synchronized intermittent mandatory ventilation. Extubation was performed when the patient fulfilling extubation criteria, hemodynamically stable, alert and proper ventilation maintained and blood gas values are within safety levels. Antibiotic and analgesics were used as the standard protocol of the institution follow. Postoperatively patients were evaluated in ICU on 0, 1st, 2nd, 3rd & 4th postoperative days for the incidence of any form of atrial arrhythmia.

STUDY FLOW CHART



CONCEPTUAL FRAMEWORK



Data collection Technique:

- Researcher himself by means of the following techniques collected data.
- Face to face interview.
- Necessary information was collected by reviewing related medical records.

Data collection Instrument:

A semi structured questionnaire was developed in English, followed by conversion to Bangle. The questionnaire was developed using the selected variables according to the specific objectives and it contained questions related to socio-demographic characteristics, preoperative, per operative and postoperative outcomes.

Data collection tools were developed by reviewing the related literature and seeking an opinion from the subject experts, research advisors, seniors, and colleagues.

Pretesting:

The preformed structured questionnaire and checklist was pre-tested on 5 patients in department of cardiac surgery, BSMMU. It was finalized after necessary modification based on pre-testing with the help of supervisor.

Quality control checks:

Data were checked immediately after completing interview and review of necessary investigation reports. Again, before data processing, collected information was checked for completeness and internal consistency considering the norms of missing data.

Statistical analysis:

- The collected data was checked, reviewed, and organized for accuracy & completeness.
- Data processing was done by the Statistical Package for Social Science (SPSS) 25th edition.
- All collected data was analyzed and interpreted by using different statistical techniques (e.g. mean, percentage, logistic regression etc.).
- The findings of the study were presented in different tables and figures.

- The continuous data was evaluated by the independent t-test and the categorical data were evaluated using the chi-square test.
- Role of NLR in prediction of in-hospital outcome were reviewed using t-test, univariate logistic regression analysis etc. depending on types of variables.
- Comparison of outcome between group A and group B were done based on few pre-fixed outcome variables and they were divided into primary outcome variable and secondary outcome variable. Primary outcome variable were in-hospital AF after OPCAB, which will be compared to evaluate any statistical significance. Secondary outcome variables viz. duration of mechanical ventilator support, duration of ICU stay, duration of hospital stay, postoperative mortality and morbidity due to thromboembolism etc. These secondary variables were also evaluated to search any statistical significance.
- p value ≤ 0.05 was considered as significant.
- The results were presented in tables and figures.

Ethical considerations:

- Ethical approval was taken from the Institutional Review Board (IRB) for conducting my thesis.
- Informed written permission was taken from each individual before starting the data collection.
- Confidentiality of the subjects was maintained by giving assurance to the respondents that the information given by them were not been disclosed and be used only for study purposes.
- The data collected was kept completely confidential and only were be used for study purposes.
- The patient had the right to agree, disagree or withdraw from the study.

Results

Distribution of patients by Age between two groups

Among study population, most of the patients were within 41-60 years age group i.e., 20 (57.1%) and 21 (60.0%) in group A and B respectively. Mean age was found 52.71 ± 11.49 years in Group A and 51.91 ± 10.04 years in Group B. There was no statistically significant difference of age distribution between two groups.

Age (years)	Group A n=35	Group B n=35	P value
Mean ± SD	52.71 ± 11.49	51.91 ± 10.04	0.757 ^{NS}

Table 1: Comparison of age distribution of the patients between two groups

n = Total number of subjects NS = Not significant

SD = Standard Deviation

Data were presented as mean ±SD

Statistical analysis was done by independent t-test p value ≤ 0.05 was considered as significant.

Distribution of patients by Sex between two groups

Table- 2 shows the distribution of patients by sex between two Groups. In Group A 80.0% of the patients were male 20.0% were female, where in group B 97.1% of the patients were male and 2.9% were female. Statistical significant difference present between two Groups in distribution of patients by sex.

Gender	Group Af (%) n=35	Group Bf (%) n=35	Total f (%)n=70	P value
Male	28 (80.0)	34 (97.1)	62 (88.6)	0.024 ^S
Female	07 (20.0)	01 (2.9)	08 (11.4)	

Table 2: Comparison of sex distribution of the patients between two groups

n = Total number of subjects S = significant (p < 0.05)

Data were expressed as frequency (f) and percentage.

Chi-square test was done to measure the level of significance. p value ≤ 0.05 was considered as significant.

Distribution of patients according to Body Mass Index between two groups

The following table-3 shows BMI class in group A and group B. 6 patients in group A and 7 patients in group B were normal and 18 patients in group A and 19 patients in group B were overweight. 11 patients in group A and 9 patients in group B were obese. Among the study population most of the patients are overweight in both group. Mean BMI was found 28.02 ± 3.30 and 27.68 ± 2.87 in group A and group B respectively. There is no significant difference in BMI between two groups.

Groups			
BMI	Group A f (%)n=35	Group B f (%)n=35	p value
Normal	06 (17.1)	07 (20.0)	
Overweight	18 (51.4)	19 (54.3)	
			0.647 ^{NS}
Obese	11 (31.4)	09 (25.7)	
Mean \pm SD	28.02 ± 3.30	27.68 ± 2.87	

Table 3: Comparison of the body mass index between two groups

n = Total number of subjects NS = Not significant

SD = Standard Deviation

Data were presented as frequency (f) and mean \pm SD. Figures in the parentheses denote corresponding %. Statistical analysis was done by independent t-test.

p value ≤ 0.05 was considered as significant.

Comparison of preoperative risk factor between two groups

Table 4 shows the distribution of data obtained by evaluating risk factors. The comparison of history of smoking, hyperlipidemia and diabetes mellitus in group A and B patients were statistically not significant ($p > 0.05$) but hypertension is found statistically significant ($p < 0.05$) between the groups.

Clinical findings	Groups		p value
	Group A f (%)n=35	Group B f (%)n=35	
Smoking	18 (51.4)	15 (42.9)	0.473 ^{NS}
Hypertension	31 (88.6)	24 (68.6)	0.041 ^S
Hyperlipidemia	14 (40.0)	09 (25.7)	0.203 ^{NS}
Diabetes Mellitus	19 (54.3)	17 (48.6)	0.632 ^{NS}

Table 4: Comparison of the preoperative risk factors between two groups

n = Total number of subjects S = significant ($p < 0.05$)

NS = Not significant (>0.05)

Data were expressed as frequency (f) and percentage.

Chi-square test was done to measure the level of significance between two groups.

p value ≤ 0.05 was considered as significant.

Distribution of patients according to preoperative routine investigations between two groups

Table 5 shows preoperative NLR was 3.70 ± 1.13 in group A and 1.90 ± 0.60 in group B and there are statistically significant differences between the groups. Mean serum creatinine was 1.07 ± 0.19 in group A and 1.07 ± 0.18 in group B. Mean Na^+ and K^+ level of group A was 139.47 ± 2.78 and 3.79 ± 0.17 and of group B was 138.25 ± 2.67 and 3.76 ± 0.19 respectively. The differences were not statistically significant.

Preoperative investigations	Groups		p value
	Mean ± SD		
	Group A n=35	Group B n=35	
NLR	3.70 ± 1.13	1.90 ± 0.60	0.001 ^S
Na ⁺ (mEq/L)	139.47 ± 2.78	138.25 ± 2.67	0.064 ^{NS}
K ⁺ (mmol/l)	3.79 ± 0.17	3.76 ± 0.19	0.946 ^{NS}
Serum Creatinine (mg/dl)	1.07 ± 0.19	1.07 ± 0.18	0.985 ^{NS}

Table 5: Comparison of the preoperative investigation between two groups

N = Total number of subjects S = Significant (p<0.05)

NS = Not significant (p > 0.05) SD = Standard Deviation

NLR = Neutrophil Lymphocyte ratio Na⁺ = Serum Sodium

K⁺ = Serum Potassium

Data were presented as mean ±SD

Independent t-test was done to compare between two groups.

Comparison of preoperative echocardiography attributes between two groups.

In preoperative echocardiography findings, mean LA diameter was 38.19 ± 2.22 mm and 38.46 ± 2.39 mm in group A and group B respectively. The mean of LVEF in group A and group B were 59.06 ± 4.30 % and 57.51 ± 4.90 % respectively. All these findings were compared by independent sample t-test and found to be statistically insignificant.

Groups			
Echocardiography attributes	Group A n=35	Group B n=35	p value
	Mean ± SD	Mean ± SD	
LA diameter (mm)	38.19 ± 2.22	38.46 ± 2.39	0.628 ^{NS}
LVEF (%)	59.06 ± 4.30	57.51 ± 4.90	0.166 ^{NS}

Table 6: Comparison of the preoperative echocardiographic attributes between two groups

n = Total number of subjects NS = Not significant (p > 0.05) SD = Standard Deviation

LA = left atrium

LVEF = left ventricle ejection fraction Data were presented as mean ±SD

Statistical analysis was done by independent t-test for continuous data

Distribution of patients in relation to per operative attributes between two groups

Table 7 shows the comparison of different per-operative findings between two groups of patients.

Among the study population, the mean number of coronary anastomosis performed in group A was 3.74 ± 0.78 and in group B was 3.86 ± 0.69, mean time for duration of surgery was 238 ± 61.4 & 227.37 ± 58.3 in group A & B respectively. Per operative atrial fibrillation was seen 02(5.7%) in group A whereas 01(2.9%) in group B. The p value of all variables were found >0.05 which was not statistically significant.

Operative Variables	Groups		p value
	Group Af (%) n=35	Group Bf (%) n=35	
Number of Bypass Graft used ^A			
2	02 (5.7)	01 (2.9)	
3	10 (28.6)	08 (26.67)	
4	18 (51.4)	21 (60.0)	
5	05 (14.3)	05 (14.3)	
Mean ± SD	3.74 ± 0.78	3.86 ± 0.69	0.52 ^{NS}

Duration of surgery(minute)^A			
Mean \pm SD	238 \pm 61.4	227.37 \pm 58.3	0.46 ^{NS}
Atrial fibrillation^B			
Yes	02 (05.7)	01 (02.9)	
			0.56 ^{NS}
No	33 (94.3)	34 (97.1)	

Table 7: Comparison of attributes during operation between two groups.

A Unpaired t-test was done to measure the level of significance.

B Chi-square test was done to measure the level of significance.

Figure within parenthesis indicates percentage.

f = Frequency, NS = Not significant.

Distribution of patients according to post-operative investigation between two groups

This table 8 shows mean and SD of postoperative ABG finding like Sodium (Na⁺), potassium (K⁺) and Calcium (Ca⁺⁺) level from 0 to 4th POD and post operative investigation like Serum Creatinine and Magnesium (Mg⁺⁺) from 0 to 3rd POD which didn't show any statistically significant difference between the groups.

Post-operative investigation	Groups		p value
	Group A n=35 Mean \pm SD	Group B n=35 Mean \pm SD	
0 POD			
Na ⁺ (mEq/l)	137.29 \pm 4.73	140.28 \pm 3.23	0.974 ^{NS}
K ⁺ (mmol/l)	3.72 \pm 0.56	3.75 \pm 0.50	0.853 ^{NS}
Ca ⁺⁺ (mmol/l)	0.98 \pm 0.12	0.99 \pm 0.13	0.740 ^{NS}
1st POD			
S. creatinine(mg/dl)	1.10 \pm 0.28	1.12 \pm 0.23	0.758 ^{NS}
Mg ⁺⁺ (mg/dl)	1.93. \pm 0.23	1.86 \pm 0.19	0.153 ^{NS}
Na ⁺ (mEq/l)	138.80 \pm 3.51	141.09 \pm 2.52	0.965 ^{NS}
K ⁺ (mmol/l)	3.95 \pm 0.45	3.93 \pm 0.33	0.836 ^{NS}
Ca ⁺⁺ (mmol/l)	1.04 \pm 0.14	1.04 \pm 0.11	0.839 ^{NS}
2nd POD			

S. creatinine(mg/dl)	1.10 ± 0.18	1.10 ± 0.19	0.979 ^{NS}
Mg ⁺⁺ (mg/dl)	1.91 ± 0.18	1.92 ± 0.18	0.774 ^{NS}
Na ⁺ (mEq/l)	140.59 ± 3.11	140.56 ± 2.89	0.950 ^{NS}
K ⁺ (mmol/l)	4.09 ± 0.34	4.05 ± 0.21	0.611 ^{NS}
Ca ⁺⁺ (mmol/l)	1.05 ± 0.14	1.07 ± 0.08	0.487 ^{NS}
3rd POD			
S. Creatinine(mg/dl)	1.11 ± 0.14	1.05 ± 0.12	0.06 ^{NS}
Mg ⁺⁺ (mg/dl)	1.94 ± 0.18	1.94 ± 0.22	0.931 ^{NS}
Na ⁺ (mEq/l)	140.63 ± 2.93	140.76 ± 1.98	0.830 ^{NS}
K ⁺ (mmol/l)	4.10 ± 0.32	4.12 ± 0.21	0.801 ^{NS}
Ca ⁺⁺ (mmol/l)	1.08 ± 0.12	1.09 ± 0.08	0.595 ^{NS}
4th POD			
Na ⁺ (mEq/l)	140.86 ± 2.16	140.86 ± 1.97	0.990 ^{NS}
K ⁺ (mmol/l)	4.15 ± 0.55	4.19 ± 0.15	0.664 ^{NS}
Ca ⁺⁺ (mmol/l)	1.07 ± 0.09	1.11 ± 0.81	0.104 ^{NS}

Table 8: Comparison of the post-operative investigations between two groups

n= total number of subjects NS = Not significant

SD= Standard Deviation

Data were expressed as Mean ± SD.

Independent t-test was performed to compare between two groups. p value ≤0.05 was considered as significant.

Distribution of patients according to post-operative AF between two groups

This table shows new onset of PoAF which were noted from operative day to 4th POD. 28 (80%) patients of group A and 02 (5.7%) patients of group B had postoperative atrial fibrillation after operation which was statistically significant.

Groups			
	Group Af (%) n=35	Group Bf (%) n=35	p value
PoA F			
Yes	28 (80)	02 (5.7)	0.001 ^S
No	07 (20)	33 (94.3)	

Table 9: Comparison by new onset of postoperative AF between two groups

n = Total number of subjects

PoAF = Post operative Atrial fibrillation S = Significant (p < 0.05)

Data were expressed as frequency (f) and percentage Fisher's exact test was done to compare between groups.

Chi-square test was done to measure the level of significance.

Distribution of patients in relation to post-operative outcomes between two groups

Table 10 shows the comparison of postoperative parameters like duration of ventilator used, duration of inotropic support, ICU stay and hospital stays between group A and group B patients. The Mean duration of ventilator used in group A and B were 388.29 ± 151.05 hours and 310.71 ±

151.045 minutes respectively which was statistically significant. Duration of inotropic support was also found statistically significant between the groups. Mean duration of ICU stay of group A and B was 06.06 ± 1.26 days and 5.34 ± 0.80 days respectively. The differences between duration of ICU stay were statistically significant. Mean hospital stays of group A was 10.86 ± 1.54 days and group B was 9.86 ± 1.33 days which was statistically significant.

Post-operative outcomes	Groups		p value
	Group Af (%) n=35 Mean ± SD	Group Bf (%) n=35 Mean ± SD	
^A Duration of ventilator support (minute)	388.29 ± 151.05	310.71 ± 151.045	0.024 ^S
^A Duration of inotropic support (days)	04.14 ± 1.12	3.51 ± 1.17	0.025 ^S

^A Duration of ICU stay (days)	06.06 ± 1.26	5.34 ± 0.80	0.006 ^S
^A Hospital stays (days)	10.86 ± 1.54	9.86 ± 1.33	0.005 ^S
^B Thromboembolism			
No	31 (88.6)	35 (100)	
Morbidity	04 (11.6)	00 (00)	
Mortality	00 (00)	00 (00)	0.114 ^{NS}

Table 10: Comparison of the post-operative outcomes between two groups

n= total number of subjects S = Significant

NS = Not significant

SD = Standard Deviation

Data were expressed as Mean ± SD.

Statistical analysis was done by A independent t-test and B Fischer’s exact test p value ≤0.05 was considered as significant.

Analysis of predictors of immediate post-operative atrial fibrillations

The relationship between baseline predictors and in-hospital post-operative atrial fibrillation were assessed by the use of binary logistic regression analysis. The model contained three variables (sex, HTN and NLR). The full model containing all predictors was statistically significant indicating that the model was able to distinguish between respondents who reported and did not report PoAF. Among the variables, the preoperative NLR level was found to be the only predictor (OR 5.649, 95% CI 2.353 – 13.562, p=0.001S). The model as a whole explained between 35.4% (Cox and Snell R square) and 47.5% (Nagelkerke R squared) of the variance in PoAF status, and correctly classified 80% of cases. As shown in Table 11, only one of the variables made a unique statistically significant contribution to the model (NLR). The strongest predictor of reporting a postoperative atrial fibrillation was neutrophil to lymphocyte ratio, recording an odds ratio of 5.649. This indicated that respondents who had raised neutrophil to lymphocyte ratio were over 5.5 times more likely to report postoperative atrial fibrillation

than those who did not have raised neutrophil to lymphocyte ratio, controlling for all other factors in the model.

Variables	B	S.E.	Wald	df	p value	OR	95 % CI for OR	
							Lower	Upper
SEX	0.514	0.914	0.316	01	0.574 ^{NS}	1.671	0.279	10.018
HTN	0.195	0.757	0.066	01	0.797 ^{NS}	1.215	0.276	5.351
NLR	1.732	0.447	15.017	01	0.001 ^S	5.649	2.353	13.562
CONSTANT	-5.739	1.739	10.893	01	0.01	0.003		

Table 11: Logistic Regression Analysis of predictors of PoAF

PoAF = Post operative Atrial Fibrillation

HTN = Hypertension

NLR = Neutrophil to Lymphocyte Ratio

S = Significant ($p < 0.05$)

NS = Non significant ($p > 0.05$)

CI = Confidence Interval

OR = Odds Ratio

S.E. = Standard Error

Discussion

Mean age of both groups was 52.71 ± 11.49 and 51.91 ± 10.04 years respectively. Mostly patients were advanced aged group i.e., > 50 years. But mean difference was not statistically significant. Similar types of study were conducted by Celik and his associates. They also revealed in their study that, advanced age (62.4 ± 9.6 vs 64.5 ± 9.2) was not statistically significant (0.364) between the groups as a predictor of PoAF (Celik E et al. 2020).

Out of 70 study patients who underwent off pump coronary artery bypass grafting 88.6% were male and 11.4% were female. Sex distribution of the patients were statistically significant between two groups ($p=0.024$). 80% were male in group A and in group B, 97.1% were male. Gibson and his associates found 81% & 87.9% of their study cases in male gender groups respectively, Celik and associates found 80.6% of their study cases in male gender group which are consistent to the findings of this study (Gibson PH et al. 2010; Celik E et al. 2020). From this data we revealed that coronary artery diseases are more common in male population.

Gibson and his associates demonstrated that, mean BMI of patients of both study group were 29.05 and 28.2. On contrary we found almost 28.02 & 27.68 populations in our study group which were not statistically significant. Here we almost correlate with study published by Gibson and his associates (Gibson PH et al. 2010).

We found no significant difference between risk factors such as DM, Smoking, Hyperlipidemia which corresponds to the findings of Celik and colleagues (Celik E et al. 2020) but there was a significant difference between HTN i.e. p value 0.041 which failed to corresponds to Celik and colleagues but correlates with Gibson and colleagues (Gibson PH et al. 2010) i.e. p value 0.02.

Among the preoperative echocardiographic parameters LA size and LVEF were considered for comparison between the two groups. Mean LA size of group A was 38.19 ± 2.22 and group B was 38.46 ± 2.39 mm. Mean LVEF of group A was 59.06 ± 4.30 % and group B was 57.51 ± 4.90 %. The difference between the groups were not statistically significant ($p= 0.628$, $p=0.166$) respectively. Erdolu and his associates found preoperative LVEF p value was 0.761 and LA p value was 0.447 which supports our study (Erdolu B et al. 2020).

In our study pre operative investigation like S. Creatinine, S. Sodium and S. Potassium had p value 0.985, 0.064 and 0.946 which were not statistically significant where as NLR shows mean 3.70 ± 1.13 in group A and 1.90 ± 0.60 in group B with the p value 0.001 which is statistically significant and nearly

corresponds to the study of Celik and associates which demonstrate mean NLR 2.7 ± 1.1 & 2.2 ± 0.8 with p value 0.01 (Celik E et al. 2020).

In our study 51.4% of group A and 60.0% patients of group B were given 4 conduits for bypass with a mean value of number of graft was 3.74 ± 0.78 and 3.86 ± 0.69 with p value 0.52 where as Gibson and colleagues demonstrated mean number of bypass grafts was 3 in study and control group with p value 0.460 which signify that there was no significant difference between the group (Gibson PH et al. 2010).

In this study there was no statistically significant difference between both groups in terms of post operative investigation like S. Creatinine, S. Magnesium, Sodium, Potassium and calcium monitored upto 4th POD. However, duration of ICU & hospital stay is longer in group A than group B with p value 0.006 and 0.005 respectively which was consistent with the study done by Erdolu and his associates (Erdolu B et al. 2020). There were 4 morbidity due to thromboembolism in group A with p value 0.114 in this study which was not statistically significant.

Postoperative atrial fibrillation is the commonest arrhythmia observed in 18-40% of patients after isolated coronary artery bypass surgery (El-Chami 2010; Ozturk 2019), 35-40% after isolated valvular surgeries and even higher from 35% to greater than 60% after combined coronary artery bypass graft (CABG) and valve surgery (Greenberg J et al. 2017) which may leads to hemodynamic disturbances associated with increased risk of embolism, heart failure, prolong hospital stay and increase cost.

In our study, univariate analysis showed that NLR significantly was higher in patients with PoAF. The preoperative NLR level was found to be the only predictor (OR 5.649, 95% CI

2.353 – 13.562, $p=0.001$ S) with the sensitivity of 70 % and specificity of 87.5 % which nearly coincide with the study done by Celik and associates. Correlation studies between NLR and development of AF conducted by Gibson and colleagues showed that the rate of AF development was higher in patients with a high NLR value, which is used as an inflammatory marker (Gibson PH et al. 2010). Also, in the study by Celik and associates, preoperative NLR was independently associated with POAF with 75% sensitivity and 83% specificity (Celik E et al. 2020). The model as a whole explained between 35.4% (Cox and Snell R square) and 47.5% (Nagelkerke R squared) of the variance in PoAF status, and correctly classified 80% of cases. The relationship between inflammatory biomarkers and cardiovascular disease has been demonstrated in many studies. Among these, NLR, which is a frequently researched biomarker, is cheap and easy to obtain. In a study investigating the prognostic significance of NLR in cardiac surgery, high NLR was associated with increased early-term complications and long-term mortality rates (Erdolu B et al. 2020). Research has shown that NLR can predict AF after OPCABG.

Conclusion

This study observed that high neutrophil lymphocyte ratio level triggers postoperative atrial fibrillation after off pump coronary artery bypass grafting. Postoperative atrial fibrillation was significantly higher among those with high neutrophil to lymphocyte ratio (≥ 2.63) group. From this study we can conclude that there is association between neutrophil to lymphocyte ratio and postoperative atrial fibrillation. So early detection of high neutrophil to lymphocyte ratio level will be helpful in early prediction of occurrence of postoperative atrial fibrillation and effective measures could be taken for prevention of its complication after off pump coronary artery bypass grafting.

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