Galore International Journal of Health Sciences and Research
Vol. 8; Issue: 2; April-June 2023
Website: www.gijhsr.com
Original Research Article *P-ISSN: 2456-9321*

Association of Total Leucocyte Count and Neutrophil to Lymphocyte Ratio with Short Term Major Adverse Cardiac Events after Acute ST Elevation Myocardial Infarction in a Tertiary Care Centre in South India

Dr Amrita Kurian[1], Dr Poornima H[2], Dr Abdul Salam[3]

[1]Junior Resident, Department of Internal Medicine, Government T D Medical College, Kerala University of Health Sciences, Alappuzha, India
[2]Professor, Department of Internal Medicine, Government T D Medical College, Kerala University of Health Sciences, Alappuzha, India
[3]Assistant Professor, Department of Cardiology, Government T D Medical College, Kerala University of Health Sciences, Alappuzha, India

Corresponding Author: Dr Amrita Kurian

DOI: https://doi.org/10.52403/gijhsr.20230206

ABSTRACT

Ischemic Heart Disease is a global health issue with developing countries bearing the brunt of the burden. The development of adverse cardiac events after an acute coronary event further aggravates the morbidity and mortality. In a developing country like India, employing inexpensive markers such as Total Leucocyte Count (TLC) and Neutrophil to Lymphocyte Ratio (NLR) can greatly aid prognostication in acute myocardial infarction.

The study aimed at estimating the association of TLC and NLR with short term Major Adverse Cardiac Events (MACE) after acute STEMI. We also studied the association of Total Leucocyte Count and Neutrophil to Lymphocyte ratio with TIMI (Thrombolysis in Myocardial Infarction) score.

This hospital based descriptive study that spanned over a year enrolled 270 patients admitted under General Medicine and Cardiology with STEMI. TLC and NLR were measured within 24 hours of admission. The subjects were followed up for MACE (namely heart failure hospitalization, compensated systolic dysfunction, arrhythmias, non-fatal reinfarction/stroke, and cardiovascular death) at the end of 1 week and 1 month.

Among the 270 cases, 107 developed MACE after 1 week and 89 developed MACE after 1 month. The most common MACE was LV systolic dysfunction followed by arrhythmias. There was a significant association between NLR and MACE after 1 week (p value:0.04). Similarly, there was a positive association between NLR and TIMI score (p value:0.002).

The association between total leucocyte count and MACE was not statistically significant.

We concluded that NLR, a routine, easily available test was effective in predicting major adverse cardiac events after 1 week in acute STEMI.

Keywords: *Acute Coronary Syndrome; ST elevation myocardial infarction; Total leucocyte count; Neutrophil to Lymphocyte Ratio; Major Adverse Cardiac Events; Thrombolysis in Myocardial Infarction Score (TIMI score); LV systolic dysfunction*

INTRODUCTION

Acute Coronary Syndrome (ACS) is the leading cause of death globally. In addition, the disease leads to high morbidity and loss of disability adjusted life years (DALY). [(1)]

Patients with acute coronary syndrome commonly are classified into two groups to

facilitate evaluation and management, namely patients with ST-segment elevation myocardial infarction (STEMI) and those with non-ST-segment elevation acute coronary syndrome (NSTEACS). The latter includes patients with non-ST-segment elevation myocardial infarction (NSTEMI), who, by definition, have evidence of myocyte necrosis, and those with unstable angina (UA), who do not. [(2)]

Major Adverse Cardiac Events (MACE) is a broad term that encompasses heart failure hospitalisations, compensated systolic dysfunction (LVEF </= 40%), cardiac arrhythmias, stroke, non-fatal reinfarction, and all-cause mortality. [(3)]

The pathophysiology of ACS is extremely heterogeneous. In most cases, the underlying mechanism is obstruction of coronary artery blood flow by a thrombus that results from rupture or erosion of an underlying atherosclerotic plaque. Less common causes are MI with non-obstructive coronary arteries, coronary artery dissection, coronary artery spasm, and coronary microvascular dysfunction.

Inflammation is a key factor in atherosclerotic plaque progression and its subsequent fate. Recent studies have shown that increased levels of certain inflammatory markers like high sensitive CRP, lipoprotein phospholipase A2, interleukin, selectin molecules, adhesion ligands etc. in patients with Acute Myocardial Infarction are associated with increased number of cardiovascular complications and a higher incidence of death. [(4-7)] However, most of these markers are not universally available and their cost is high. In a developing country like India, where public health centres are the sole resort of low-income patients, their usefulness is limited in day-to-day clinical practice.

Total leucocyte count and NLR are inexpensive, universally available tests that are routinely done in all admitted patients. So, if a positive association can be established between TLC and NLR at admission and short term major adverse cardiac events after STEMI, these parameters can be used for prognostication in acute MI, thus aiding in identifying patients at a higher risk of morbidity and mortality.

TIMI (Thrombolysis In Myocardial Infarction) Score [(8)] is a universally accepted score to determine the likelihood of ischemic events or mortality in patients with ACS. The study will be considering TIMI Score as the gold standard in estimating the risk of MACE after acute STEMI against which the lab parameters namely TLC and NLR ratio will be compared.

OBJECTIVES

Primary objective:

To study the association of Total Leucocyte Count and Neutrophil to Lymphocyte Ratio at admission with short term (at the end of 7 days and 30 days) major adverse cardiac events in patients with acute ST Elevation Myocardial Infarction (STEMI).

Secondary objective:

To study the association of Total Leucocyte Count and Neutrophil to Lymphocyte ratio with TIMI (Thrombolysis In Myocardial Infarction) score.

MATERIALS & METHODS

CASE DEFINITION:

Patients with unstable angina based on clinical history and examination, who meet the established specific ECG criteria for the diagnosis of ST-elevation MI [(2)] who present to hospital within 24 hours of symptom onset.

STUDY DESIGN: Hospital based Descriptive study.

STUDY POPULATION: Patients admitted with acute STEMI as per case definition in Medicine wards, Medicine Intensive Care Unit, Cardiology ward and Intensive Coronary Care Unit of Government T D Medical College, Alappuzha.

STUDY DURATION: December 2021 to December 2022.

INCLUSION CRITERIA: All patients in the age group 25-70 years meeting the case definition.

EXCLUSION CRITERIA:

- Established cases of chronic kidney disease, chronic liver disease, cerebrovascular accidents and other terminal illnesses since they already have a high risk of mortality.
- Presentation with fever, recent infection within one-week, recent trauma, recent surgical intervention within 1 month, malignancies, myeloproliferative disorders are all conditions resulting in leucocytosis and hence were excluded.
- Patients receiving immunosuppressants since many of these drugs result in leukopenia.
- Patients with Ischaemic Dilated Cardiomyopathy, idiopathic cardiomyopathies, severe valvular heart diseases and major congenital heart diseases.
- Patients who underwent heart transplant or coronary artery bypass graft.

SAMPLING METHOD – Convenience sampling

SAMPLE SIZE ESTIMATION – In the reference study, prevalence of a major adverse cardiac event, say LV systolic dysfunction in the population with elevated TLC was 60%. [(9)] Hence by the formula 4×p×q/ d^2 (where p is prevalence, q is 1- p and d i.e., precision is 10% of p) sample size would be 270 subjects.

STATISTICAL ANALYSIS

Data collected was entered in MS Excel spreadsheet and data analysed using IBM SPSS Statistics software version 29.0.

Qualitative variables were expressed as proportions and percentages. Quantitative variables as mean ± standard deviation. The categorical variables in both groups were compared using the Chi square test to ascertain if the two groups were homogenous with respect to the variables. Fisher's test was used to determine association between categorical variables and Mann-Whitney U test was employed to study the association between continuous variables. For all the statistical interpretations, $p<0.05$ was considered significant.

RESULTS

1. Patient demographics

Among a total of 270 subjects 93% belonged to an age group between 46 and 70 whereas only 7% belonged to an age group between 25 and 45. Thus, the percentage of young STEMI in the study population was 7%.

68.1% were men while 31.9% were women.

66.3% of the study population had a normal BMI whereas 3.3% were obese. Pre-obese subjects constituted 4.4% while overweight subjects amounted to 25.9%. 26.7% of the subjects were active smokers while another 26.7% were reformed smokers.

Figure 1: DISTRIBUTION OF COMORBIDITIES AMONG STUDY SUBJECTS

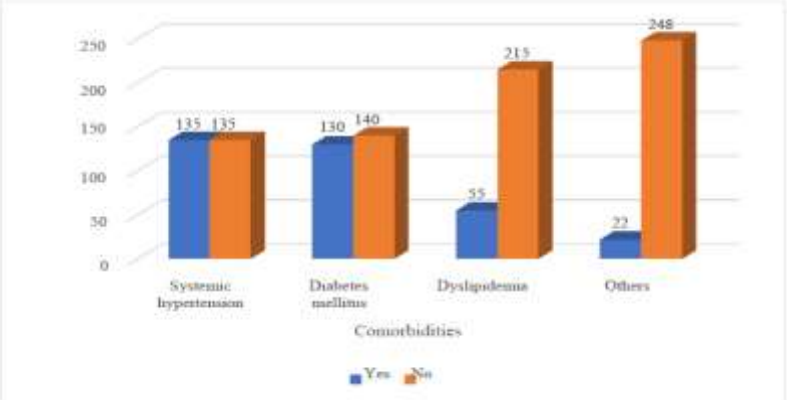

Table 1: DISTRIBUTION OF SUBJECTS BASED ON HISTORY OF ISCHEMIC EVENT

H/O Ischemic Event	Frequency	Percent
None	213	78.9
Coronary event with good LV function	31	11.5
Non coronary event without residual deficits	22	8.1
Coronary with good LV function & non coronary without residual deficits	4	1.5
Total	270	100.0

2. Clinical presentation

24 STEMI cases presented with a systolic blood pressure less than 90 mm of Hg of which 18 progressed to cardiogenic shock. [(10)]

The most common site of acute myocardial infarction was anterior wall (34.8%) followed by inferior wall (18.5%) and infero-posterior wall (12.2%). Only 6.7% had extensive anterior wall MI.

Most of the patients (83.3%) belonged to Killip Class 1 whereas Killip class 3 and 4 amounted to 9.3%.

3. Laboratory profile

A vast majority of patients (65.6%) had leucocytosis at presentation and only 34.4% had a normal WBC count, in concordance with various literature. [(9, 11-14)]

Among 270 subjects, the distribution based on NLR was almost equal with 50.4% subjects having NLR less than 4 and 49.6% having it more than or equal to 4.

4. Management and complications

Figure 2: DISTRIBUTION OF SUBJECTS BASED ON MODE OF ACUTE MANAGEMENT

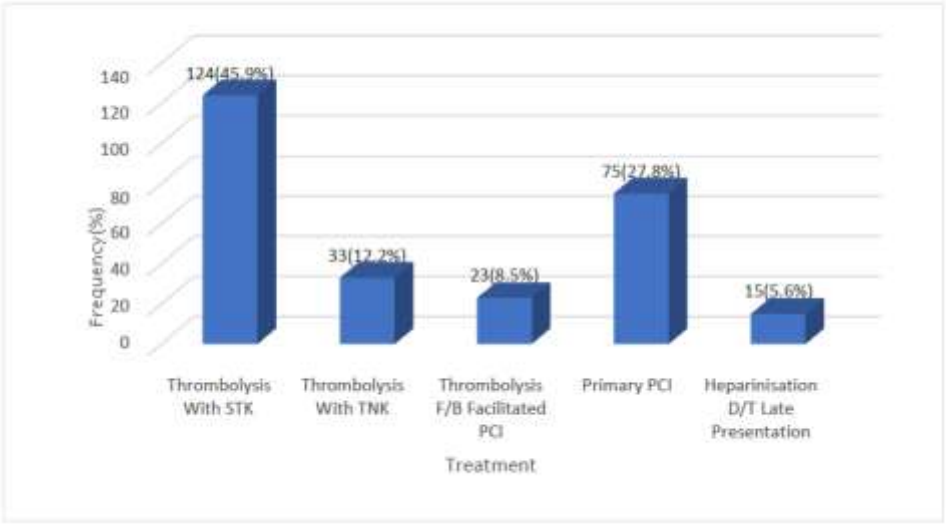

Table 2: DISTRIBUTION OF SUBJECTS ACCORDING TO MAJOR ADVERSE CARDIAC EVENTS AFTER 1 WEEK

MACE after 1 week	Frequency	Percent
LV Systolic Dysfunction	54	20.0
Heart Failure	15	5.6
Bradyarrhythmias	25	9.3
Tachyarrhythmias	6	2.2
Death	6	2.2
VSR (Ventricular Septal Rupture)	1	0.4
Stroke	0	0
Reinfarction	0	0
Total	107	39.6

Table 3: DISTRIBUTION OF SUBJECTS ACCORDING TO MAJOR ADVERSE CARDIAC EVENTS AFTER 1 MONTH

MACE after 1 month	Frequency	Percent
LV Systolic Dysfunction	49	18.1
Heart Failure	8	3.0
Reinfarction	1	0.4
Bradyarrhythmias	21	7.8
Tachyarrhythmias	5	1.9
Death	4	1.5
*VSR	1	0.4
Stroke	0	0
Total	89	33.0

* This is the same patient who had developed VSR at the end of first week. She was awaiting surgery when reassessed at the end of the month.

5. Testing the association between variables

The incidence of all 6 major adverse cardiac events after one week was observed to be high in patients with leucocytosis, yet a statistically significant association could not be proved. The Fisher's exact test p value was found to be 0.253. Even at the end of the month, a significant association between leucocytosis and MACE remained elusive with a Fisher's exact test p value of 0.112. However, the incidence of MACE was still higher in patients with leucocytosis.

Table 4: ASSOCIATION BETWEEN TOTAL COUNT AND MACE AFTER ONE WEEK

MACE after 1 week	Total Count		Total
	</= 10,000	>10,000	
LV Systolic Dysfunction	21	33	54
Heart Failure	3	12	15
Bradyarrhythmias	4	21	25
Tachyarrhythmias	2	4	6
Death	1	5	6
VSR	0	1	1
Total	31	76	107

Table 5: ASSOCIATION BETWEEN LEUCOCYTOSIS AND MACE AFTER ONE MONTH

MACE after 1 month	Total Count		Total
	</= 10,000	>10,000	
LV SystolicDysfunction	17	32	49
Heart Failure	1	7	8
Reinfarction	0	1	1
Bradyarrhythmias	2	19	21
Tachyarrhythmias	2	3	5
Death	0	4	4
VSR	0	1	1
Total	22	67	89

On the other hand, a significant association did exist between NLR and MACE after one week. The Fisher's exact test p value was 0.04.

Table 6: ASSOCIATION BETWEEN NLR AND MACE AFTER ONE WEEK

MACE after 1 week	NLR		Total
	<4	>/=4	
LV Systolic Dysfunction	20	34	54
Heart Failure	6	9	15
Bradyarrhythmia	14	11	25
Tachyarrhythmia	4	2	6
Death	0	6	6
VSR	0	1	1
Total	44	63	107

The significant association that was proven between the 2 parameters after 1-week period could not hold true for longer periods as no association could be established between NLR values and MACE after 1 month. The Fisher's exact test p value was 0.221.

Table 7: ASSOCIATION BETWEEN NLR AND MACE AFTER ONE MONTH

MACE after 1 month	NLR		Total
	<4	>/=4	
LV SystolicDysfunction	17	32	49
Heart Failure	2	6	8
Reinfarction	0	1	1
Bradyarrhythmia	11	10	21
Tachyarrhythmia	4	1	5
Death	2	2	4
VSR	0	1	1
Total	36	53	89

A statistically significant association could be observed between high NLR and high TIMI score (p value=0.002). Also, higher TIMI scores were observed in subjects having both leucocytosis and high NLR (p value=0.002). But there existed no significant association between leucocytosis and high TIMI score.

Table 8: ASSOCIATION BETWEEN TIMI AND NLR

		TIMI		P value (Mann- Whitney U)
		Mean	Std. Deviation	
Total Count	</= 10,000	2.42	1.740	0.103
	>10,000	2.97	2.277	
NLR	<4	2.34	1.679	0.002
	>/=4	3.23	2.415	

DISCUSSION

A total of 270 patients who met the inclusion and exclusion criteria were enrolled in this descriptive study. There was male predominance among patients with STEMI (68.1%). 79.6% had associated comorbidities with hypertension being the most common modifiable risk factor (seen in 50% of patients). As for the site of acute STEMI, there was anterior wall preponderance (34.8%) followed by inferior wall (18.5%). Majority of the patients (83.3%) belonged to Killip class I. 18 patients presented in Killip class IV of which 4 succumbed to death. The most frequently employed management strategies were thrombolysis with streptokinase (45.9%) and primary PCI (27.8%).

65.6% of the enrolled patients had a total count more than 10,000 while 34.4% had a

count less than or equal to 10,000 which was in accordance with the literature cited. [9, 11-14] 50.4% had NLR < 4 whereas 49.6% had NLR ≥ 4. Interestingly, 37.4% of the population had both leucocytosis and a raised NLR.

Among the 270 patients, the most frequently observed MACE at the end of 1 week was compensated LV systolic dysfunction (20%), followed by bradyarrhythmia (9.3%) and heart failure hospitalisations (5.6%). 6 patients succumbed to death during the 1st week and the rare complication of ventricular septal rupture (VSR) was observed in 1 patient. None of the study subjects developed reinfarction or stroke. Similar observations were made by Devendra Kumar et al, [9] where among 100 cases of acute MI, 15 patients developed LV dysfunction and 7 died during the in-hospital period. Another study by Agha Fahad revealed heart failure as the most frequent MACE (an incidence of 45.5%) [15]

At the end of 1 month, 18.1% had compensated LV systolic dysfunction, 7.8% had bradyarrhythmia and 3% patients had readmission for heart failure. 4 more patients expired during the course of the month. The patient who had developed VSR was awaiting surgical repair when followed up after 1 month. Among 270 patients, only 1 patient developed reinfarction while none of the study subjects developed stroke.

Even though 76 of the 107 patients who developed major adverse cardiac events after 1 week had leucocytosis, a statistically significant association could not be proven between Total Leucocyte Count and MACE at the end of 1 week (p value = 0.253). Among 6 deaths at the end of 1 week, 5 had leucocytosis. This contradicted the observations of Agha Fahad Jan et al, who showed a positive association between high leucocyte count and in hospital heart failure incidences and mortality. [15] Sharma et al had also demonstrated that patients with higher TLC had a 2-fold increase in hospital mortality [14]

Similar was the association between leucocytosis and MACE at the end of 1 month. 65% of the LV systolic dysfunctions, 85% of arrhythmias and all 4 deaths had leucocytosis at admission. But the p value for association wasn't statistically significant (0.112) as opposed to a study by Hal V Barron who had concluded that patients with high TLC at admission were 3 times more likely to die at 30 days period. [12]

On the contrary, there was a significant association between NLR and MACE after one week (p value =0.04). A M Adam et al, also had similar conclusions that MACE-positive patients demonstrate a significantly higher values of NLR at admission (NLR > 3.5) [13] However, this association couldn't be established between NLR and MACE at the end of one month (p value =0.221) High NLR group had a higher incidence of LV systolic dysfunction and heart failure hospitalisations, similar to the observations of Dong et al, [16] but the incidence of arrhythmias was more in population with a normal NLR.

The study also proved a significant association between NLR and TIMI score (p value=0.002). Patients with a high TIMI score had an elevated NLR at admission. But there was no significant association between leucocytosis and TIMI score.

Meta-analysis by Dong et al had pointed out that the prognostic role of NLR in predicting MACE or mortality was obvious only in researches with a large sample size. Studies with a small sample size(< 500), could not establish a significant association. [16] In a systematic review by Barry S Coller, the association between leucocyte count and mortality after MI was less dramatic in patients who underwent reperfusion or early revascularization treatment than in those who did not receive these therapies. [17] He also noted that additional factors like efficacy of therapy and the relative abilities of the heart to withstand infarction also account for this observed difference. Thus, regardless of the

mechanism underlying the association between leucocytosis and mortality after acute myocardial infarction, it appeared that modern reperfusion and early revascularization strategies mitigate or eliminate the association between WBC count and mortality during the first 6 months after a myocardial infarction.

The fact that most of the patients in our study underwent early revascularization (188 patients underwent revascularization within 6 hours and 67 within 6-12 hours of index pain) could be a reason why a significant association could not be established between total leucocyte count and short term MACE after STEMI.

Likewise, a small sample size would have attributed to the inability of NLR to predict MACE at the end of 1 month.

CONCLUSION

Majority of the patients who developed acute STEMI had pre-existing modifiable risk factors with systemic hypertension being the most common risk factor.

There was anterior wall preponderance among STEMI cases.

The most frequent short-term MACE was LV systolic dysfunction at the end of 1 week and 1 month.

NLR can be used as a prognostic marker in identifying individuals at higher risk of MACE at the end of 1 week. NLR also had a positive association with TIMI score, which was kept as the gold standard in estimating the risk of MACE.

No significant association could be established between total leucocyte count and MACE. This could be attributed to the early revascularisation therapy in patients and a small sample size.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: The authors would like to express their sincere gratitude to Dr Suresh Raghavan, Professor and HOD, Department of General Medicine and Dr Vinayakumar, Professor and HOD, Department of Cardiology for providing all the facilities to carry out this research.

We also acknowledge Dr Vishwakala and Mr Vidhu, Department of Preventive and Social Medicine, for assisting with the statistical analysis.

Our heartfelt gratitude goes out to all the participants of this study for their cooperation.

Source of Funding: None

The investigations incorporated in the study were a part of the routine blood examination recommended by the institutional protocol for all inpatients. The participants didn't have to bear any additional expense.

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
2. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018 Nov 13;138(20):e618–51.
3. Ch D, Zm W, Sy C. Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: A systematic review and meta-analysis. Clinical biochemistry [Internet]. 2018 Feb [cited 2023 Jan 23];52. Available from: https://pubmed.ncbi.nlm.nih.gov/29132766/
4. Bodí V, Facila L, Sanchis J, et al. Short-Term Prognosis of Patients Admitted for Probable Acute Coronary Syndrome without ST-Segment Elevation. Role of New Myocardial Damage Markers and Acute-Phase Reactants. Rev Esp Cardiol. 2002 Aug 1;55(8):823–30.
5. Sanchis J, Bodí V, Llácer À, et al. Usefulness of C-reactive protein and left ventricular function for risk assessment in survivors of acute myocardial infarction. The American Journal of Cardiology. 2004;94(6):766.
6. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and

inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000 Oct 19;343(16):1139–47.
7. Bodí V, Sanchis J, Llácer À, et al. Prognostic Markers of Non-ST Elevation Acute Coronary Syndromes. Rev Esp Cardiol. 2003 Sep 1;56(9):857–64.
8. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000 Oct 24;102(17):2031-7. doi: 10.1161/01.cir.102.17.2031. PMID: 11044416.
9. Agarwal D, Singhal A, Singhal P, et al. Prognostic Importance Of WBC Count In Acute Myocardial Infraction. International Journal of Medical and Biomedical Studies. 2020 Jun 30;4.
10. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. New England Journal of Medicine. 2012 Oct 4;367(14):1287–96.
11. Núñez J, Fácila L, Llàcer À, et al. Prognostic Value of White Blood Cell Count in Acute Myocardial Infarction: Long-Term Mortality. Revista Española de Cardiología (English Edition). 2005 Jun 1;58(6):631–9.
12. Barron HV, Harr SD, Radford MJ, et al. The association between white blood cell count and acute myocardial infarction mortality in patients ≥65 years of age:
13. Adam AM, Rizvi AH, Haq A, et al. Prognostic value of blood count parameters in patients with acute coronary syndrome. Indian Heart J. 2018;70(2):233–40.
14. Sharma B. Prognostic Importance of WBC Count in Acute Myocardial Infraction.
15. International Journal of Medical and Biomedical Studies. 2022 Mar 28;6.
16. Jan AF, Habib S, Naseeb K, et al. High Total Leukocyte Count And Heart Failure After Myocardial Infarction. 2011;44(1).
17. Dong CH, Wang ZM, Chen SY. Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: A systematic review and meta-analysis. Clin Biochem. 2018 Feb;52:131–6.
18. Coller BS. Leukocytosis and Ischemic Vascular Disease Morbidity and Mortality: Is It Time to Intervene? ATVB. 2005 Apr;25(4):658–70.

How to cite this article: Amrita Kurian, Poornima H, Abdul Salam. Association of total leucocyte count and neutrophil to lymphocyte ratio with short term major adverse cardiac events after acute ST elevation myocardial infarction in a tertiary care centre in South India. *Gal Int J Health Sci Res*. 2023; 8(2): 27-34. *DOI: https://doi.org/10.52403/gijhsr.20230206*

|******