IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 8 Ser. 11 (August. 2019), PP 41-58
www.iosrjournals.org

Relationship Between Neutrophil To Lymphocyte Ratio(NLR) And Fragmented QRS in acuteSTEMI Patients Treated With Thrombolysis.

Dr.Balaji Thenrajan[1], Dr.Selayan Kalaichelvi[2].
(Senior assistant professor, Department of Medicine, Govt. Royapettah Hospital, Kilpauk Medical College, Chennai-14, India)[1].
(Associate professor, Department of Medicine, Govt. Royapettah Hospital, Kilpauk Medical College, Chennai-14, India)[2].
Corresponding Author: Dr. Selayan Kalaichelvi.

Abstract:*Acute coronary syndrome (ACS) is a major cause of morbidity and mortality worldwide where inflammation plays a very important role in the pathogenesis. Studies have shown that neutrophilia and lymphocytopenia along with Neutrophil to lymphocyte ratio(NLR) a recent and novel prognostic marker in ACS[1]. It is economical and easily obtainable from the routine complete blood count. Fragmented QRS in a 12 lead electrocardiogram was proven to be a novel marker[2]. Fragmented QRS complexes are novel ECG signals which are associated with varied conduction abnormalities and the delay of peri- infarct conductions due to myocardial scarring or necrosis[2]and develops mostly within 48 hours during acute myocardial infarction[3]. Some studies also point out that presence of a fragmented QRS might be more specific marker of a previous ischemic event when compared to the age-old, time tested and well known _Q' wave[6].NLR can be a cheap alternative though the specificity might be on the lower side[8,9,10,11]. There was one study published demonstrating the relationship between fragmented QRS and Neutrophil to Lymphocyte ratio previously. Hence,this study demonstrated the relationship between the two in patients treated withpercutaneous coronary intervention (PCI)[12]. Here in our resource limited situation, we might not have access to a primary PCI and an urgent thrombolysis might be the only solution. There has been no study documented which describes the fragmented QRS in thrombolysed patients. Thus, we aim to investigate the relationship between NLR and fQRS in ST segment elevation myocardial infarction (STEMI) patients undergoingthrombolysis.*

Keywords: *Acute coronary syndrome- fragmented QRS-neutorphil to lymphocyte ratio-thrombolysis-STEMI.*

Date of Submission: 12-08-2019 Date of Acceptance: 26-08-2019

I. Introduction

Acute coronary syndrome (ACS) is a major cause of morbidity and mortality worldwide. Inflammation plays a very important role in the pathogenesis of ACS as evidenced by the raised inflammatory parameters seen associated with the disease. White blood cell (WBC) count predicts the risk of ACS, is a well proven fact[1] . However there are certain subtypes and other related parameters of the WBC count that has shown stronger association with the prognosis. Studies have shown that neutrophilia is significantly associated with poor outcomes in an ACS. Other studies have shown that lymphopenia is also an accompaniment in ACS[1]. Therefore combining these two parameters and finding the Neutrophil to lymphocyte ratio was thought about.That makes the neutrophil to lymphocyte ratio (NLR) a recent and novel prognostic marker[1]. It is economical and easily obtainable from the routine complete blood count. Among all WBC subtypes, NLR is shown the strongest predictor of inflammatory state and predicts poor outcomes in patients with ACS, and hence found to be a better markerwhen compared to neutrophilia andlymphopenia.

A 12 lead electrocardiogram still remains a very important investigation in the diagnosis of Acute Coronary Syndrome. Various prognostic markers have been described in the ECG in patients with ACS. Fragmented QRS is such a novel marker[2]. Insimple terms additional notches within the QRS complex without a typical bundle branch block can be taken as fragmented QRS. Fragmented QRS complexes are novel ECG signals which are associated with varied conduction abnormalities and the delay of peri- infarct conductions due to myocardial scarring or necrosis[2]. It originatesfrom heterogeneous ventricular activation due to myocardial ischemia or scarring and develops mostly within 48 hours during acute myocardial infarction[3]. Another concept is fragmented QRS arises from myocardial scars[4]. Previous studies demonstrated that systemic inflammation may be associated with the development of fQRS. Ever since fragmented QRS was linked to poor prognosis of ACS in the landmark study by Das *et al*, alot of studies have emerged, linking fQRS to various entities including

arrhythmias and aneurysms[5,6,7]. However its role in predicting previous ischemic event is well established now. Some studies also point out that presence of a fragmented QRS might be more specific marker of a previous ischemic event when compared to the age-old, time tested and well known ‗Q' wave[6]. Various studies also described the association of fragmented QRS with complications of ACS including in-hospital mortality and reduced ejection fraction[7]. There are many structured scales for prognosticating acute coronary syndromes. Nonetheless, either neutrophil to lymphocyte ratio or fragmented QRS have emerged in any of them. Further studies are required to identify the importance of these two very simple and inexpensive tools and probably incorporate them into routine practice for risk stratification and triage ofpatients.

There have been studies conducted linking other markers of inflammation viz. hsCRP to fragmented QRS. However CRP is relatively expensive and might not be afeasible option in resource limited conditions. NLR can be a cheap alternative though the specificity might be on the lower side[8,9,10,11]. There was one study published demonstrating the relationship between fragmented QRS and Neutrophil to Lymphocyte ratio previously. However there have been no Indian studies for the same. This study demonstrated the relationship between the two in patients treated withpercutaneous coronary intervention (PCI)[12]. Here in our resource limited situation, we might not have access to a primary PCI and an urgent thrombolysis might be the only solution. There has been no study documented which describes the fragmented QRS in thrombolysed patients. Thus, we aim to investigate the relationship between NLR and fQRS in ST segment elevation myocardial infarction (STEMI) patients undergoingthrombolysis.

II. Materialsand methods

a. Study design:- Cross-sectional observational study
b. Study period:- 6 months
c. Study area: - Tertiary health care centre.

STUDY POPULATION

d. Consecutive patients admitted in Government RoyapettahHospital with new acute onset STEMI in a time period of 6 months wouldbe included in the study. The diagnosis of STEMI would be based on ECGand Echo findings.

SAMPLE SIZE

Sample size was calculated using the EpiInfo Application issued by the Center forDisease Control, America. The expected frequency of fragmented QRS in patients withhigh neutrophil to lymphocyte ratio averages to 70%. Assuming 70% as expected frequency with 6% MOE and 95% Confidence level, the total sample size is 225.

Assuming a non-response rate of 10%, the final sample size is decided as 250.

INCLUSION CRITERIA

Any patient admitted with new acute ST elevation myocardial infarctionundergoing thrombolysis. ST elevation MI will be defined as an ST elevation 1 mm inany two or more adjacent precordial or limb leads with Echocardiogram showing aregional wall motion abnormality in the corresponding wall.

EXCLUSION CRITERIA

1. Patients already diagnosed with Coronary Artery Disease
2. Patients with complete or incomplete Bundle Branch Blocks
3. Medical conditions that could affect the WBC counts (acute or chronic infection orinflammatory diseases, hematologic disorder, malignancies, end-stage liver orrenal disease, and use of steroid therapy or chemotherapy)
4. Contraindication for thrombolysis
5. Patients with pathological Q waves presenting with or without symptoms
6. Acute MI presenting as new onset LBBB

III. Methodology

Patients admitted in the ICCU with a diagnosis of new onset STEMI based on ECG,meeting the inclusion criteria were included in the study. Patients were asked to fill a semi-structured pre-tested questionnaire to collect information regarding patientdemographics, risk factors and co-morbidities. This was used for subset analysis.

Physical examination was performed to rule out comorbid illness. Old medical recordswere reviewed. Twelve lead ECGs of all patients were taken on admission, afterthrombolysis, and at the 24th and 48th hours

after admission. ECG was standardized to10 mm/mV height amplitude, 25 mm/s speed, and 0.16–100 Hz filter range.

Electrocardiographic analyses were performed by a cardiologist. Percentage of STsegment resolution (STR) was measured by the following formula: (Sum of ST elevationson pre-lysis ECG) − (Sum of ST elevations on post-lysis ECG) / (Sum of ST elevationson pre-lysis ECG) × 100, so total ST segment elevation before and after thrombolysiswas calculated. Pathological Q wave, in our study was defined as any Q wave in leadsV2–V3 ≥ 0.02 seconds or QS complex in these leads, and a Q wave ≥0.03 seconds andN0.1 mV or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of acontiguous lead grouping (I, aVL; V1–V6; II, III, aVF). fQRS was defined as anadditional R wave, notching of the R wave, notching of the downstroke or upstroke of theS wave, or more than one R' without a typical bundle branch block. Patients having fQRSat 48th hours ECGs were defined as fQRS (+) group, and patients not having fQRS at48th hours irrespective of the on admission ECG were defined as fQRS (−) group. Thelast available ECG was used for the presence of fQRS in case of in-hospital mortality.The number of leads with ST-segment elevation (STE) and ST-segment depression(STD) and number of leads with fQRS were recorded. CBCs of all patients were taken immediately after admission and before starting anymedical therapy. Total counts for WBC (and for its subtypes) were evaluated using anautomated blood cell counter. NLR was calculated for each patient as the ratio of theneutrophil-to-lymphocyte counts. Other biochemical parameters, including serumcreatinine, lipid profile were measured with standard laboratory methods.

Echocardiography was performed on all patients. Thrombolysis was initiated if nototherwise contraindicated. Anticoagulant and antiplatelet therapies were given to allpatients according to guidelines.

IV. Results

The collected data were analysed with IBM.SPSS statistics software 23.0 Version.To describe about the data descriptive statistics frequency analysis, percentage analysiswere used for categorical variables and the mean & S.D were used for continuousvariables. To find the significant difference between the bivariate samples in Independentgroups the Unpaired sample t-test was used. To find the significance in categorical dataChi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2tables then the Fisher's Exact was used. In all the above statistical tools the probabilityvalue .05 is considered as significant levelA total of 253 subjects were included in the study of which 105 were females and148 were males. The mean age of presentation was 66.19 ± 11.15. 31.2% of the patientswere in the age group of 60-69 years. 7.1% of the population was in the age group of 40-49 years. A statistically significant association was found with age and presence of fQRS (P<0.001). Out of the 31 subjects who were 80 years or older, 28 had evidence of fQRS. There was no statistically significant relation between any sex and fQRS.

Table 5: Age distribution

		Frequency	Percent
Valid	40 - 49 yrs	18	7.1
	50 - 59 yrs	66	26.1
	60 - 69 yrs	79	31.2
	70 - 79 yrs	59	23.3
	> = 80 yrs	31	12.3
	Total	253	100.0

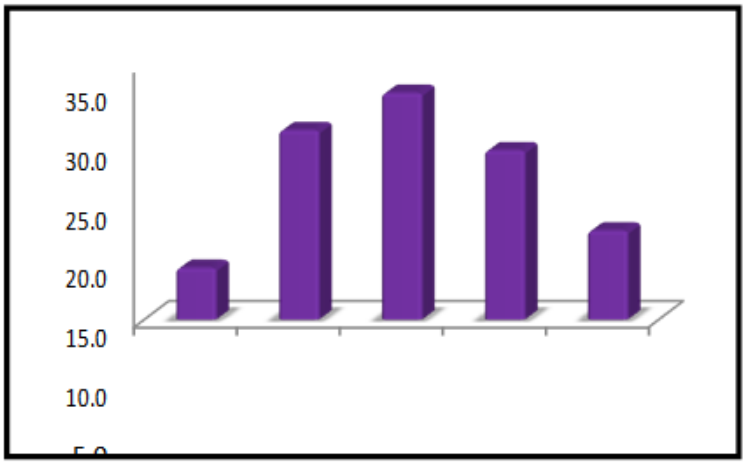


Fig 9: Age range distribution percentage

Table 6: Mean, SD of age in the study population

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	253	40	91	66.19	11.151
Valid N (listwise)	253				

Table 7: Age and fQRS

			FQRS		Total
			FQRS -	FQRS +	
AGE	40 - 49 yrs	Count	9	9	18
		% within FQRS	7.8%	6.5%	7.1%
	50 - 59 yrs	Count	31	35	66
		% within FQRS	27.0%	25.4%	26.1%
	60 - 69 yrs	Count	41	38	79
		% within FQRS	35.7%	27.5%	31.2%
	70 - 79 yrs	Count	31	28	59
		% within FQRS	27.0%	20.3%	23.3%
	> = 80 yrs	Count	3	28	31
		% within FQRS	2.6%	20.3%	12.3%

Table 8: Age and fQRS, Chi-Square tests

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	18.734[a]	4	.001
Likelihood Ratio	21.678	4	.000
Linear-by-Linear Association	5.354	1	.021
N of Valid Cases	253		

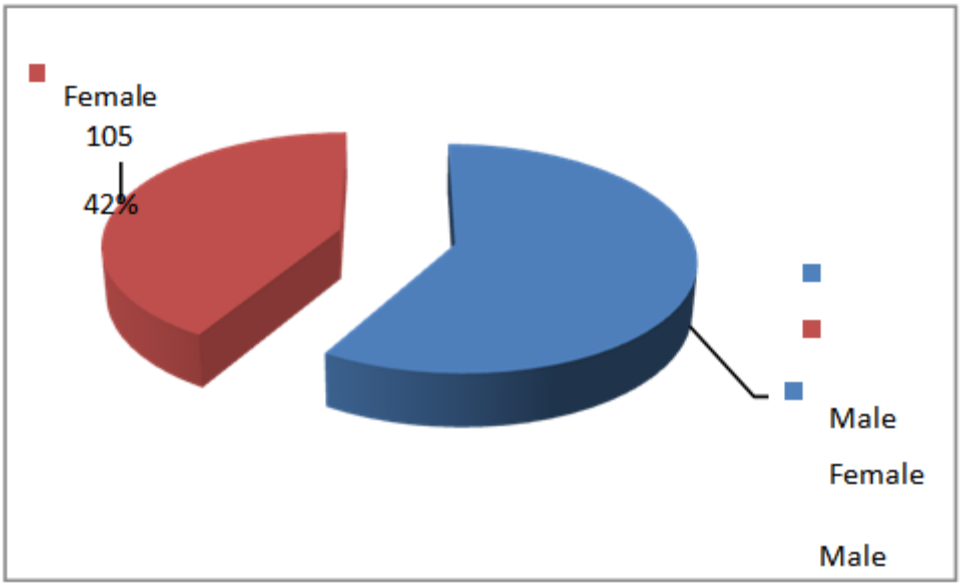


Fig 10: Sex Distribution

Table 9: Sex* fQRS Crosstab

			FQRS		Total
			FQRS -	FQRS +	
Sex	Male	Count	43	61	104
		% within FQRS	37.4%	44.2%	41.1%
	Female	Count	72	77	149
		% within FQRS	62.6%	55.8%	58.9%
Total		Count	115	138	253
		% within FQRS	100.0%	100.0%	100.0%

Table 10: Sex Distribution

	FQRS -	FQRS +
Female	37.4%	44.2%
Male	62.6%	55.8%

Table 11: Chi-Square Tests, Gender*fQRS

	Value	df	Asymp.Sig.(2-sided)	ExactSig. (2-sided)	ExactSig. (1-sided)
Pearson Chi-Square	1.202[a]	1	.273		
Continuity Correction[b]	.937	1	.333		
Likelihood Ratio	1.205	1	.272		
Fisher's Exact Test				.306	.167
Linear-by-Linear Association	1.197	1	.274		
N of Valid Cases	253				

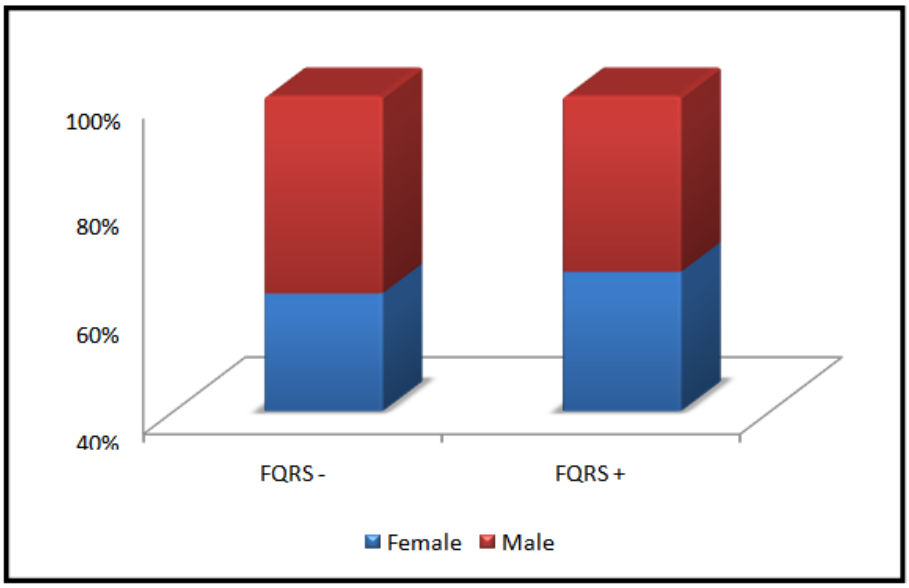


Fig 11: Sex distribution in both groups

Out of the 253 subjects, 116 were diabetic of whom 69 had evidence of fQRS. No statistically significant association was found. Similarly a total of 133 subjects were hypertensives, of which 51.4% had presence of fQRS and statistically significant association could be shown. Of the 7 seven patients who had a previous history of cerebrovascular accident, 5 had presence of fQRS. 7 patients had history of chronic kidney disease of which 3.6% had presence of fQRS.

Table 12: T2DM and fQRScrosstable

			FQRS		Total
			FQRS -	FQRS +	
T2DM	Absent	Count	68	69	137
		% within FQRS	59.1%	50.0%	54.2%
	Present	Count	47	69	116
		% within FQRS	40.9%	50.0%	45.8%
Total		Count	115	138	253
		% within FQRS	100.0%	100.0%	100.0%

Table 13: Distribution of diabetics among the two groups

	FQRS -	FQRS +
Absent	59.1%	50.0%
Present	40.9%	50.0%

Table 14: T2DM and fQRS; Chi-Square tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.106[a]	1	.147		
Continuity Correction[b]	1.755	1	.185		
Likelihood Ratio	2.111	1	.146		
Fisher's Exact Test				.164	.093
Linear-by-Linear Association	2.098	1	.148		
N of Valid Cases	253				

Fig 12: Distribution of diabetics in both the groups

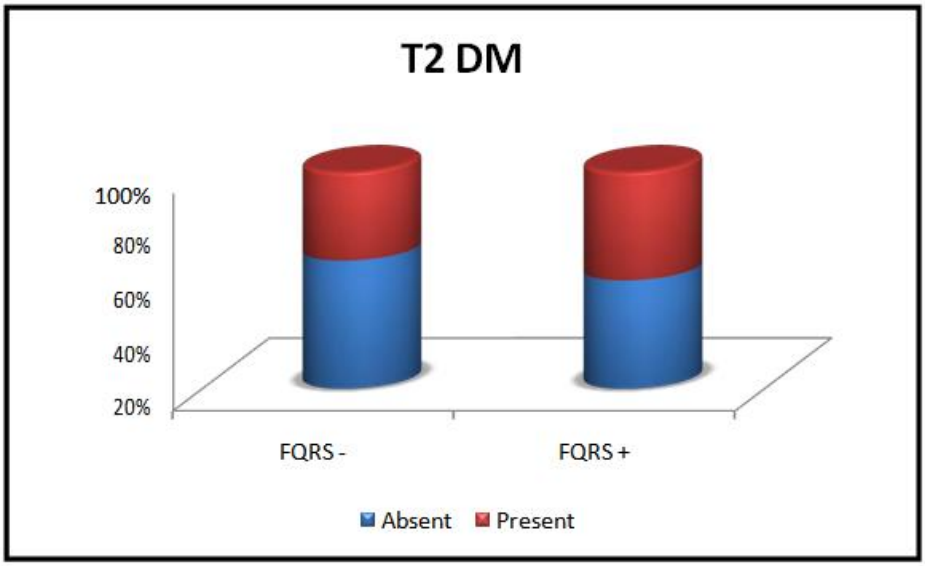


Table 15: Systemic hypertension and fQRS

			FQRS		
			FQRS -	FQRS +	Total
SHT	Absent	Count	53	67	120
		% within FQRS	46.1%	48.6%	47.4%
	Present	Count	62	71	133
		% within FQRS	53.9%	51.4%	52.6%
Total		Count	115	138	253
		% within FQRS	100.0%	100.0%	100.0%

Table 16: Systemic hypertension: distribution in both groups

	FQRS -	FQRS +
Absent	46.1%	48.6%
Present	53.9%	51.4%

Table 17: systemic hypertension and fQRS

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.153[a]	1	.696		
Continuity Correction[b]	.070	1	.792		
Likelihood Ratio	.153	1	.696		
Fisher's Exact Test				.706	.396
Linear-by-Linear Association	.152	1	.697		
N of Valid Cases	253				

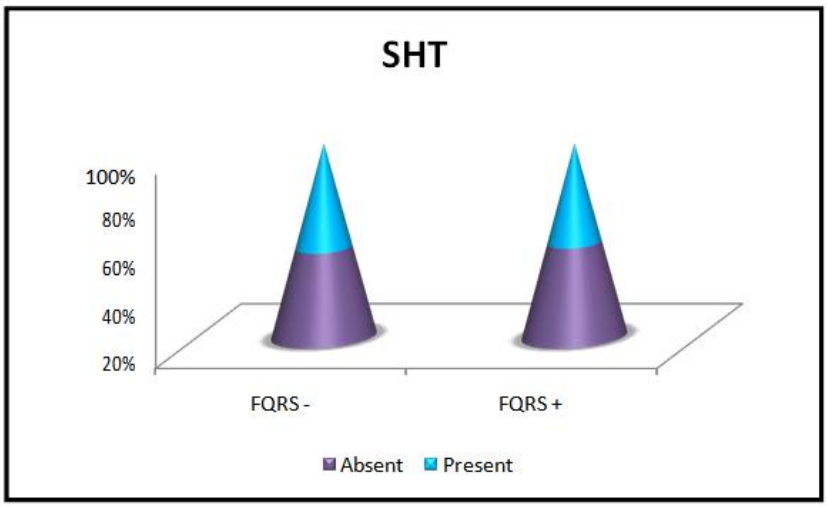


Fig 13: Distribution of Systemic Hypertension in both groups

Table 18:CVA and fQRS

			FQRS		
			FQRS -	FQRS +	Total
CVA	Absent	Count	113	133	246
		% within FQRS	98.3%	96.4%	97.2%
	Present	Count	2	5	7
		% within FQRS	1.7%	3.6%	2.8%
Total		Count	115	138	253
		% within FQRS	100.0%	100.0%	100.0%

Table 19: Distribution if CVA

	FQRS -	FQRS +
Absent	98.3%	96.4%
Present	1.7%	3.6%

Table 20: Chi-Square tests – CVA and fQRS

	Value	df	Asymp.Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.828[a]	1	.363		
Continuity Correction[b]	.275	1	.600		
Likelihood Ratio	.862	1	.353		
Fisher's Exact Test				.460	.305
Linear-by-Linear Association	.824	1	.364		
N of Valid Cases	253				

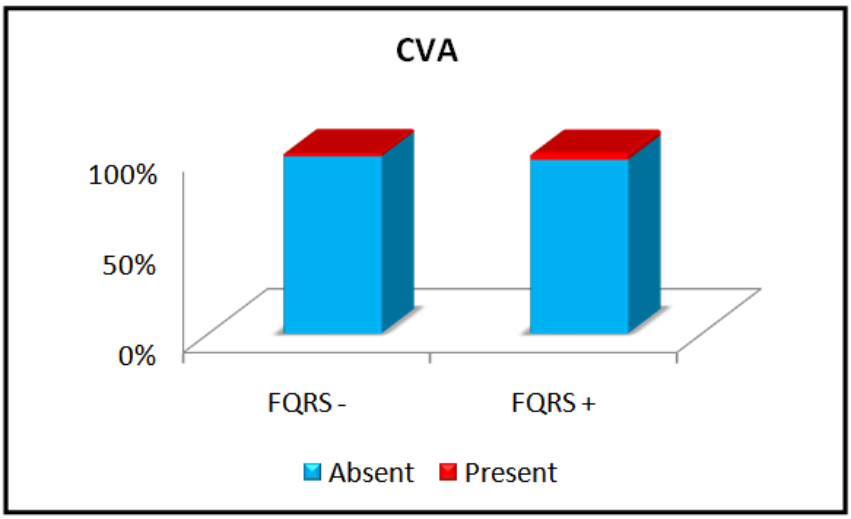


Fig 14: Distribution of CVA

Table 21: CKD and fQRS

			FQRS		Total
			FQRS -	FQRS +	
CKD	Absent	Count	113	133	246
		% within FQRS	98.3%	96.4%	97.2%
	Present	Count	2	5	7
		% within FQRS	1.7%	3.6%	2.8%
Total		Count	115	138	253
		% within FQRS	100.0%	100.0%	100.0%

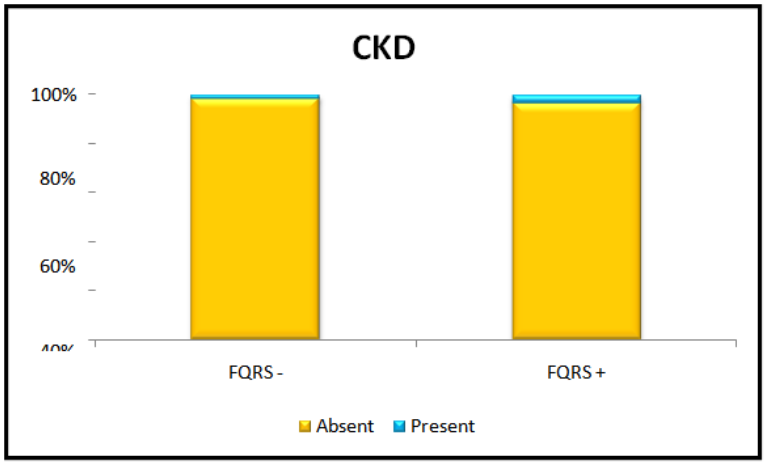
Table 22: Distribution of CKD

	FQRS -	FQRS +
Absent	98.3%	96.4%
Present	1.7%	3.6%

Table 23: Chi-Square tests – CKD and fQRS

	Value	df	Asymp. Sig.(2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.828[a]	1	.363		
Continuity Correction[b]	.275	1	.600		
Likelihood Ratio	.862	1	.353		
Fisher's Exact Test				.460	.305
Linear-by-Linear Association	.824	1	.364		
N of Valid Cases	253				

Fig 15: Distributon of CKD



The mean length of hospital stay was 5.75± 1.114 days for the fQRS+ group and 5.74±1.109 for the fQRS- group.

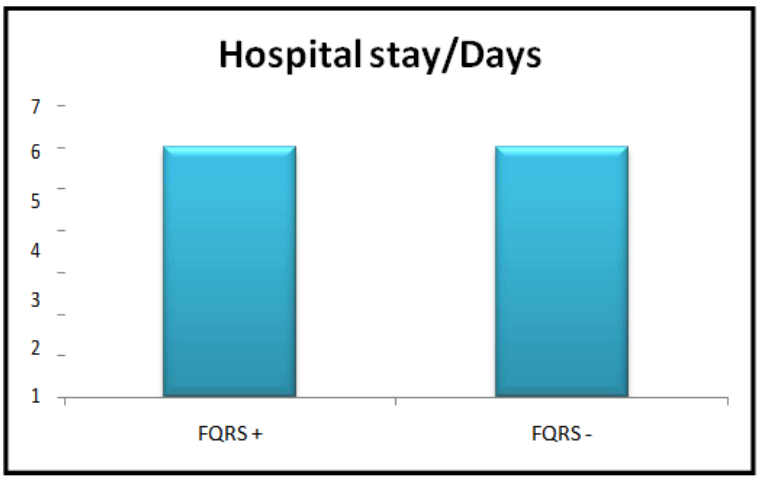


Fig 16: Mean length of hospital stay

The mean duration of chest pain was 4.17 ± 2.38 days for the fQRS+ group and 4.38±2.50 for the fQRS- group.

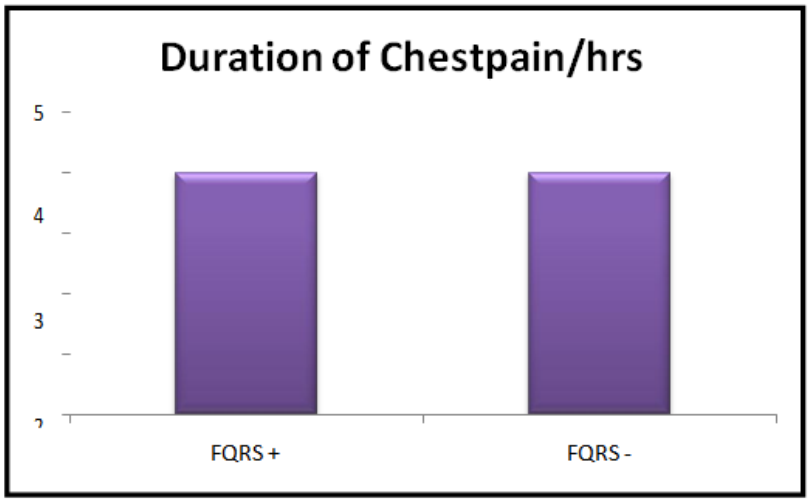


Fig 17: Mean duration of chest pain

The BMI was 24.56 ± 3.40 days for the fQRS+ group and 24.77±3.87 for the fQRS- group.

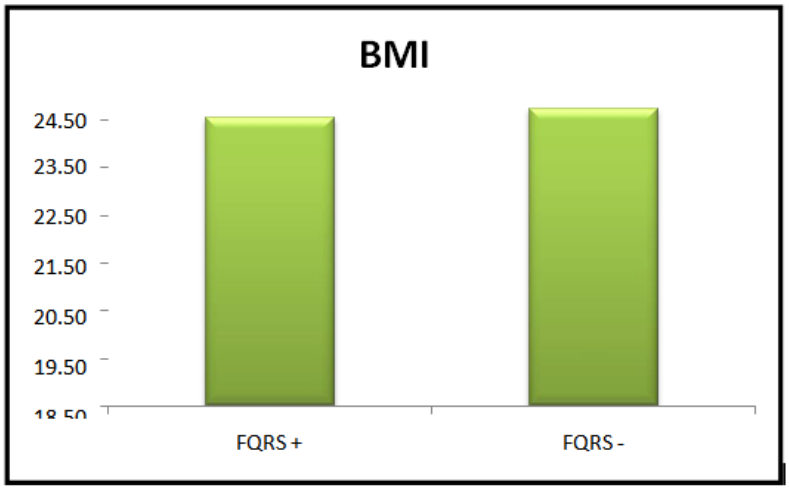


Fig 18: Mean BMI

The mean leucocyte count was 7932.04 with a SE of ±115.66 for the fQRS+ group and 7877.53 with a standard error±110.19 for the fQRS- group.

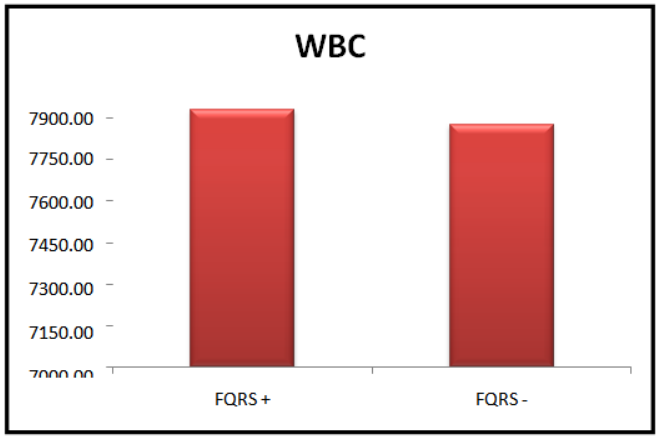


Fig 19: Mean WBC count

The mean neutrophil count was 5978.83 with a standard error of 93.52 for the fQRS+ group and 5430.70 with a standard error±96.75 for the fQRS- group.

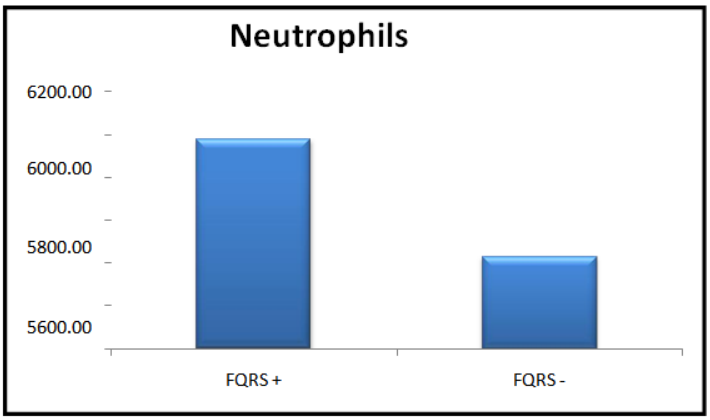


Fig 20: Mean neutrophil count

The mean lymphocyte count was 5978.83 with a standard error of 93.52 for the fQRS+ group and 5430.70 with a standard error±96.75 for the fQRS- group.

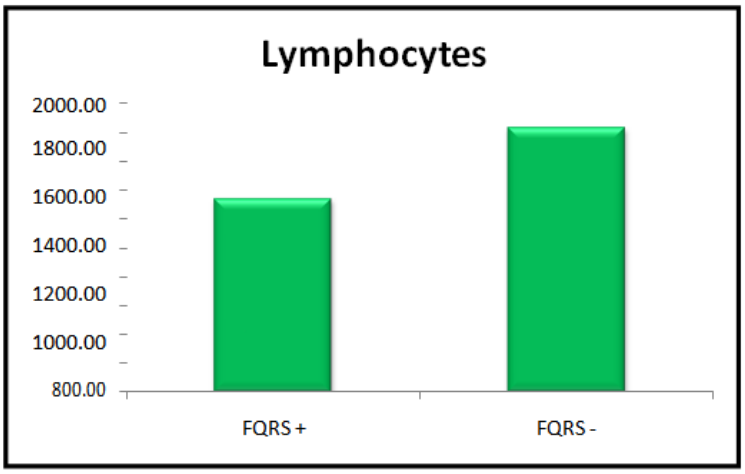


Fig 21: Mean lymphocyte count

The mean NLR was 4.70 ± 1.14 for the fQRS+ group and 3.19±1.07 for the fQRS-group.

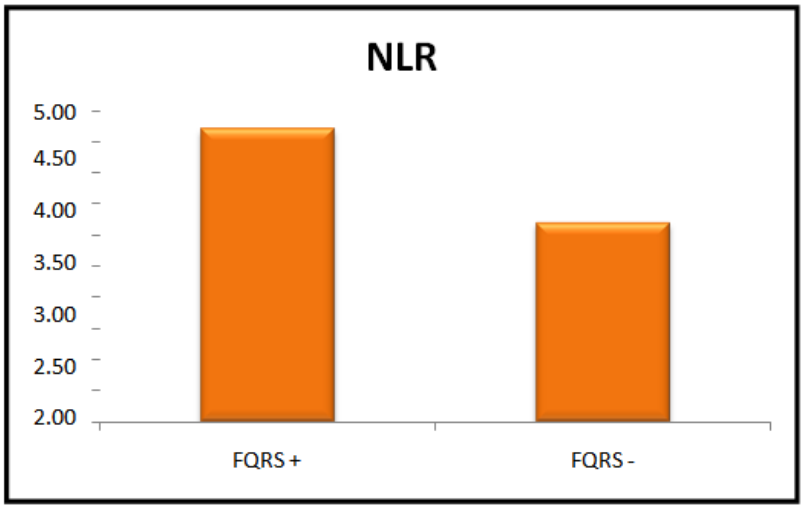


Fig 22: Mean NLR

Our patient cohort was divided into two groups according to the presence of fQRS. When patients with fQRS compared to patients with non-fQRS, baseline clinical characteristics, MI localization, and treatment modalities were similar.

Table 24: Mean, SD and SE of mean of variuos parameters in both groups

Group Statistics					
FQRS		N	Mean	Std. Deviation	Std.ErrorMean
AGE	FQRS +	138	67.62	12.130	1.033
	FQRS -	115	64.46	9.618	.897
LOS	FQRS +	138	5.75	1.114	.095
	FQRS -	115	5.74	1.109	.103
ch. Pain- DUR	FQRS +	138	4.17	2.358	.201
	FQRS -	115	4.38	2.570	.240
BMI	FQRS +	138	24.56	3.40	0.29
	FQRS -	115	24.77	3.87	0.36
WBC	FQRS +	138	7932.04	1358.70	115.66
	FQRS -	115	7877.53	1181.69	110.19
NEUTROPHILS	FQRS +	138	5978.83	1098.57	93.52
	FQRS -	115	5430.70	1037.56	96.75
LYMPHOCYTES	FQRS +	138	1341.24	382.50	32.56
	FQRS -	115	1834.79	548.57	51.15
NLR	FQRS +	138	4.70	1.14	0.10
	FQRS -	115	3.19	1.07	0.10
EF	FQRS +	138	48.36	13.201	1.124
	FQRS -	115	53.75	13.126	1.224

However, patients with fQRS had lower left ventricular ejection fraction (LVEF). The mean EF was 48.36± 1.124 for the fQRS+ group and 53.75 ± 1.224 for the fQRS- group.

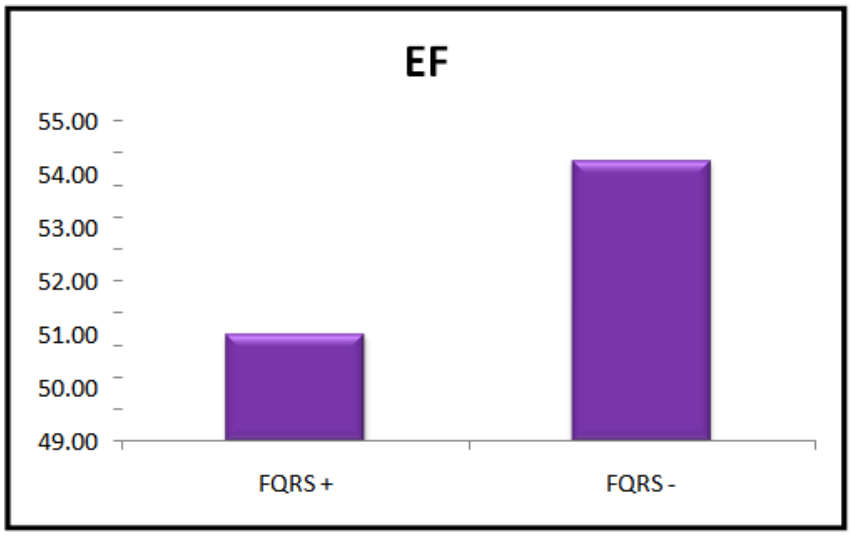


Fig 23: Mean ejection fraction in both groups

In addition, WBC, neutrophils, and NLR were significantly higher, whereas lymphocytes were significantly lower in patients with fQRS compared to patients with non-fQRS.

An NLR ≥ 3.75 was found to predict a lower EF with a specificity of 76.50% and a sensitivity of 76.10%. The frequency of fQRS and the number of leads with fQRS were significantly higher for the group with NLR ≥ 3.75. Out of the 253 subjects 120 were below the cut off and 133 were above the cut off. Out of the 120 with a low NLR 33 had presence of fQRS and out of the 133 above the cut off 105 had presencefQRS.

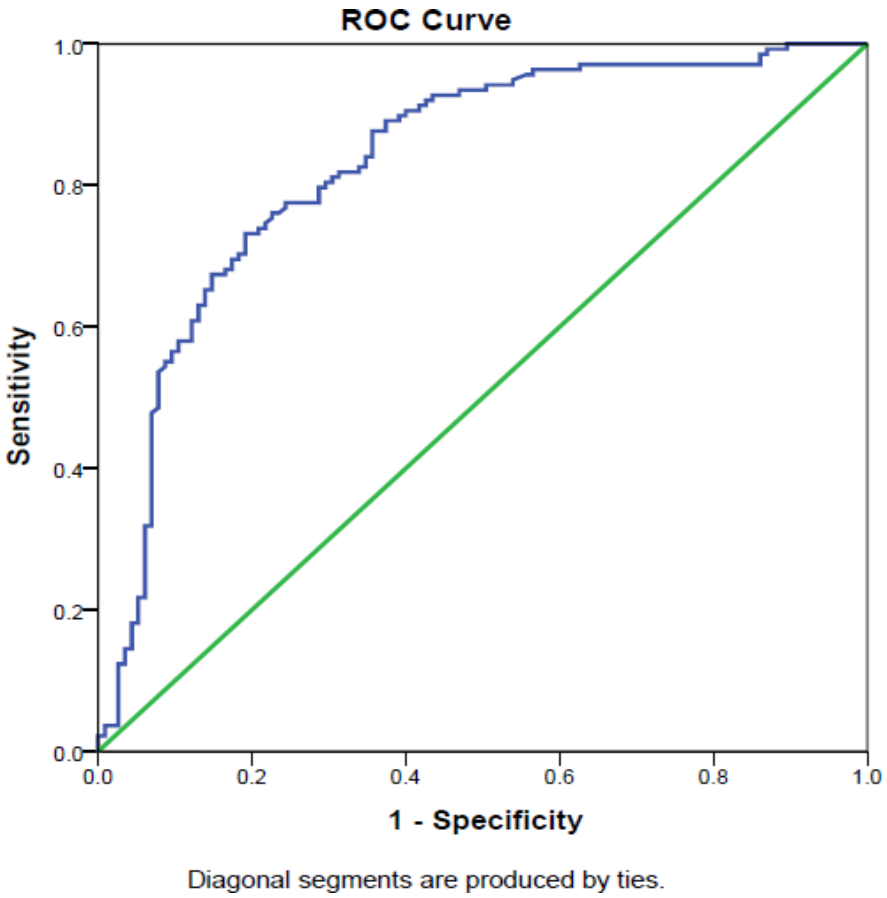


Fig 24: ROC curve for NLR

Area Under the Curve

Test Result Variable(s): NLR

Table 25: AUC of ROC for NLR

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.832	.027	.0005	.780	.884

Coordinates of the Curve		
Test Result Variable(s): NLR		
Positive if Greater Than or Equal To[a]	Sensitivity	1 Specificity
.24390	1.000	.000
1.24695	1.000	991
1.26570	1.000	983
1.50696	1.000	974
1.74923	1.000	957
1.83980	1.000	948
1.93598	1.000	939
1.97917	1.000	.930
2.00222	1.000	913
2.04469	1.000	.904
2.10729	1.000	.896
2.14683	.993	.896
2.16534	.993	.887
2.17110	.993	.878
2.18152	.993	.870
2.20222	.986	.870
2.23232	.986	.861
2.25429	.978	.861
2.28428	.971	.861
2.32840	.971	.852
2.37456	.971	.843
2.41622	.971	.835
2.43411	.971	.826
2.44060	.971	.817
2.44896	.971	.809
2.48672	.971	.800
2.52776	.971	.791
2.53803	.971	.774
2.55022	.971	.765
2.56154	.971	.757
2.58145	.971	.748
2.59940	.971	.739
2.60214	.971	.722
2.60859	.971	.713
2.61761	.971	.704
2.62395	.971	.696
2.62845	.971	.687
2.64643	.971	.678
2.66410	.971	.670
2.67677	.971	.661
2.69221	.971	.652
2.69878	.971	.635
2.70782	.971	.626
2.71761	.964	.626
2.72457	.964	.617
2.73394	.964	.609
2.73872	.964	.591
2.76242	.964	.583
2.78702	.964	.574
2.78956	964	.565
2.79123	.957	.565
2.79583	.957	.557
2.80717	.949	.539
2.81497	.942	.539
2.82263	.942	.530
2.83090	.942	.522
2.83274	.942	.513
2.83667	.942	.504
2.84857	.935	.504
2.85973	.935	.496
2.86399	935	.487
2.87727	.935	.478
2.89337	.935	.470
2.90370	.928	.470
2.91033	.928	.461
2.91389	.928	.452
2.92996	.928	.443
2.94385	.928	.435
2.95794	.920	.435
2.97381	.920	.426
2.98810	.913	.426
3.00617	.913	.417
3.01598	.906	.417
3.03064	.906	.409
3.06124	.906	.400
3.09130	.899	.400
3.10270	.899	.391
3.10736	.891	.391
3.11244	.891	.383
3.11436	.891	.374
3.12414	.884	.374

3.16430	.877	.374
3.19961	.877	.357
3.21590	.870	.357
3.23892	.862	.357
3.27641	.855	.357
3.33818	.848	.357
3.40056	.841	.357
3.43934	.841	.348
3.45196	.833	.348
3.47299	.826	.348
3.50195	.826	.339
3.51649	.819	.339
3.52374	.819	.330
3.52855	.819	.322
3.53767	.819	.313
3.56139	.812	.313
3.59735	.812	.304
3.61771	.804	.304
3.62099	.804	.296
3.63377	.797	.296
3.64888	.797	.287
3.65248	.790	.287
3.65408	.783	.287
3.65556	.775	.287
3.67787	.775	.278
3.70156	.775	.270
3.70350	.775	.261
3.70528	.775	.252
3.71012	.775	.243
3.73178	.768	.243

3.75450	.761	.235
3.76660	.761	.226
3.78710	.754	.226
3.80051	.746	.217
3.80676	.739	.217
3.84792	.739	.209
3.88611	.732	.209
3.89181	.732	.200
3.89664	.732	.191
3.89928	.725	.191
3.90833	.717	.191
3.92119	.710	.191
3.92781	.703	.191
3.93743	.703	.183
3.94844	.696	.183
3.96066	.696	.174
3.98801	.688	.174
4.01338	.681	.174
4.04000	.681	.165
4.08993	.674	.165
4.12542	.674	.157
4.13099	.674	.148
4.13616	.667	.148
4.14924	.659	.148
4.16199	.652	.148
4.17517	.652	.139
4.20989	.645	.139
4.24266	.638	.139
4.25483	.630	.139
4.27051	.630	.130

4.28314	.623	.130
4.29717	.616	.130
4.31727	.609	.130
4.34444	.609	.122
4.36402	.601	.122
4.41111	.594	.122
4.46824	.587	.122
4.48967	.580	.122
4.50318	.580	.113
4.51937	.580	.104
4.53891	.572	.104
4.54724	565	.104
4.55342	.565	.096
4.57689	.558	.096
4.60567	.551	.096
4.62019	.551	.087
4.64583	.543	.087
4.68066	.536	.078
4.69502	.529	.078
4.70881	.522	.078
4.73611	.514	.078
4.76067	.507	.078
4.78567	.500	.078
4.80179	.493	.078
4.80745	.486	.078
.83850	.478	.070
4.89719	.471	.070
4.92900	.464	.070
4.95797	.457	.070
4.99054	.449	.070

4.99722	.442	.070
5.01249	.435	.070
5.03350	.428	.070
5.12101	.420	.070
5.33307	.413	.070
5.47006	.406	.070
5.48011	.399	.070
5.49064	.391	.070
5.50044	.384	.070
5.50715	.377	070
5.51942	.370	.070
5.53089	.362	.070
5.54293	.355	.070
5.56111	.341	.070
5.57114	.333	.070
5.58167	.326	.070
5.61691	.319	.070
5.65467	.319	.061
5.66550	.312	.061
5.66909	.304	.061
5.67504	.297	.061
5.67968	.290	.061
5.68986	.275	.061
5.70441	.268	.061
5.71252	.261	.061
5.71530	.254	.061
5.72289	.246	.061
5.73561	.239	.061
5.74122	.232	.061
5.74312	.225	.061

5.74734	.217	.061
5.75529	.217	.052
5.76091	.210	.052
5.77402	.203	.052
5.78761	.196	.052
5.79322	.188	.052
5.80111	.181	.052
5.81460	.181	.043
5.82628	.167	.043
5.83378	.159	.043
.84481	.152	.043
5.85313	.145	.043
5.86451	.145	.035
5.88030	.138	.035
5.89852	.130	.035
5.92151	.123	.035
5.93948	.123	.026
5.94750	.116	.026
5.96074	.109	.026
5.99925	.101	.026
6.02740	.094	.026
6.04375	.087	.026
6.06205	.080	.026
6.06956	.072	.026
6.07917	.065	.026
6.08558	.058	.026
6.11364	.051	.026
6.15187	.043	.026
6.16548	.036	.026
6.16879	.036	.017

6.21171	.036	.009
6.28605	.029	.009
6.42783	.022	.009
6.53976	.022	0.000
6.54348	.014	0.000
6.72175	007	0.000
7.90000	0.000	0.000

Table 26: Co-ordinates of ROC

Table 27: Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
AGE	Equal variances assumed	8.907	.003	2.264	251	.024	3.162	1.396	.412	5.913
	Equal variances not assumed			2.312	250.411	.022	3.162	1.368	.469	5.856
LOS	Equal variances assumed	.003	.957	.052	251	.959	.007	.140	-.269	.284
	Equal variances not assumed			.052	243.258	.959	.007	.140	-.269	.284
ch. Pain-DUR	Equal variances assumed	1.189	.277	-.673	251	.502	-.209	.310	-.820	.402
	Equal variances not assumed			-.668	234.150	.505	-.209	.313	-.825	.407
BMI	Equal variances assumed	.001	.974	-.468	251	.640	-.21379	.45691	-1.11367	.68608
	Equal variances not assumed			-.462	229.156	.644	-.21379	.46226	-1.12461	.69703
WBC	Equal variances assumed	1.232	.268	.337	251	.736	54.506	161.785	-264.123	373.134
	Equal variances not assumed			.341	250.527	.733	54.506	159.750	-260.118	369.129
NEUTROPHILS	Equal variances assumed	.427	.514	4.052	251	.0005	548.138	135.263	281.743	814.532
	Equal variances not assumed			4.074	247.067	.000	548.138	134.560	283.107	813.169
LYMPHOCYTES	Equal variances assumed	5.163	.024	-8.400	251	.000	-493.552	58.754	-609.265	-377.839
	Equal variances not assumed			-8.139	198.037	.0005	-493.552	60.638	-613.132	-373.973
NLR	Equal variances assumed	4.002	047	10.782	251	.000	1.511183	.140163	1.235136	1.787229
	Equal variances not assumed			10.842	247.290	.0005	1.511183	.139388	1.236643	1.785723
EF	Equal variances assumed	1.932	166	-3.239	251	.0005	-5.386	1.663	-8.660	-2.111
	Equal variances not assumed			-3.241	243.324	.001	-5.386	1.662	-8.659	-2.112

V. Discussion

Neutrophil to lymphocyte ratio and fragmented QRS are two novel markers in prognosticating STEMI. There have been many studies recently describing the importance of each. A high NLR has been associated with poor ejection fraction and high in hospital mortality. Similarly presence of fragmented QRS has been associated with poor ejection fraction, higher incidence of arrhythmias and increased mortality. There was one previous study which showed that a high NLR was associated with more leads having fQRS. Further combined presence of both high NLR and fQRS was associated with higher in-hospital mortality. Previous studies showed in patients who had resolved Q waves after an MI but with evidence of fragmentation of QRS had worse prognosis including increased risk of cardiac events. Varriale*et al* suggested the etiology of fQRS to be myocardial scar. Bayes de Luna *et al* proposed the etiology to be abnormality of late depolarized basalzones.

Zazula et al addressed the question of admission day NLR being a significant diagnostic tool. In their study it was proved that noncardiac chest pain patients reported lowest admission NLR versus ST-elevation MI patients who reported the highest NLR. Other forms of ACS ranked somewhere in between these two. NLR is cheap and easily repeatable, making it an important prospective tool in evaluation of chest pain. There also have been studies conducted linking CRP which is a marker of acute-phase inflammation with prognostication of MI. It can act as a marker for thrombus formation as well. Studies evaluating CRP and NLR in acute MI showed high levels of both and these were linked to thrombus formation as well. There was a study conducted with levels of CRP and fragmented QRS and it showed a significant relation between high levels of CRP and presence of fragmented QRS in ECG. However CRP and hsCRP are expensive and not easily available. NLR can thus be utilized as a surrogate marker for CRP and hence of thrombus formation as well as predicting high

likelihood of having a fragmented QRS in ECG.

In our study it was found that a high total leucocyte count was significantly associated with presence of fQRS. Similarly it was associated significantly with a high neutrophil count and low lymphocyte count. It showed strong association with high NLR as well. High NLR had an inverse relation with ejection fraction in both fQRS positive patients and fQRS negative patients.

A cut off value for NLR was found out to be 3.75 from our study. An NLR $\geq$ 3.75 was found to predict a lower EF with a specificity of 76.50% and a sensitivity of 76.10%. The frequency of fQRS and the number of leads with fQRS were significantly higher for the group with NLR $\geq$ 3.75. Out of the 253 subjects 120 were below the cut off and 133 were above the cut off. Out of the 120 with a low NLR 33 had presence of fQRS and out of the 133 above the cut off 105 had presence fQRS. This shows the high preponderance of patients with a high NLR to have fQRS in the ECG. The mean ejection fraction of the group with fQRS was lower than the mean ejection fraction of the group without fQRS. The cut-off value of NLR has been variable in different studies. In studies linking NLR and ACS, the cut-off values have been ranging from 3.2 to 5.7. More studies with larger sample size done from India are required to stipulate the normal range for this.

This study hence clearly underlines the importance of using NLR as a tool to prognosticate MI. However, NLR is a non-specific marker of inflammation; it has been found to be raised in various conditions ranging from chronic liver disease to acute cerebrovascular accident. An elevated NLR is seen in many conditions including hypertension, metabolic syndrome, diabetes mellitus, thyroid disorders, kidney or liver failure, malignancies including solid tumors like RCC and also in hematological malignancies, local or systemic infection

This reduces the specificity of using NLR as a sole indicator for prognostication of STEMI patients. That brings in the role fragmented QRS. It is clearly seen in this study that the mean ejection fraction of the fQRS+ group was lesser than that of fQRS- group.

The cause of fragmented QRS is a much debated topic. At first it was speculated to have arisen from myocardial scars. A later argument was that it was a result of abnormalities due to non-homogenous depolarization of ventricles. But this is not substantiated by ability of the tool - presence of fQRS to predict arrhythmias and SCD. It lacks in this aspect. Another observation in our study was the significant relation between age and fQRS. Out of the 31 subjects who were 80 years or older, 28 had evidence of fQRS. A study by Chia-Ying Liu *et al.* showed increased myocardialfibrosis associated with older age. This might explain that fQRS might actually be due to myocardial scarring.

Fragmented QRS was not found to have any significant association with any sex. It also seemed to be unaffected by diabetes, hypertension, CKD or CVA. The number of subjects in our study with CVA and CKD were too low; hence this might not be accurate. The BMI also did not have an effect of presence of fragmented QRS.It is known that hypertension frequently is present along with diabetes. This greatly amends the risk of cardiovascular events. Therefore it makes sense that well controlled hypertension would reduce cardiovascular events in diabetics when compared to non-diabetics. A patient of diabetes mellitus with hypertension should be on antihypertensive therapy. The antihypertensive agents to be considered are, but not limited to, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers, and beta-blockers. The agent of choice has to be chosen. There is a lot of controversy at present about which is the best agent for the same. However, in our study patients with co-existing hypertension and diabetes also did not show any statistically significant difference between the fQRS+ and the fQRS- group. This might be also because of the fact that the number of patients with hypertension and diabetes were less. Hence the significance of this particular finding isdubious.

Outcome prediction and risk stratification are of utmost significance in CAD management. Even though there are various scoring scales that are available in practice for risk stratification of patients with ACS, none of them really uses either NLR or fQRS. Many studies have dictated the association of these two parameters separately with poor prognosis in ACS. In this study we have shown that combining these two parameters might give a better specificity to this. However further studies are required for the same.

Demographics as seen in our study show that men were affected more than women. There was no statistically significant relation of either sex with presence of fQRS. As described above, age of 80 years or more were found to have high risk of havingfQRS.

VI. Conclusion

1. A high NLR is associated with a higher risk of having a fragmented QRS in the ECG.
2. The presence of fragmented QRS would mean a reduced ejection fraction and hence more left ventricular systolicdysfunction.
3. Fragmented QRS is most likely due to myocardial scarring and its incidence increases with age. It shows the importance of inflammation and scarring in the pathogenesis ofSTEMI.
4. fQRS is hence a cheap tool and doesn't require a special equipment, technique or expertise – it is always lying in the ECG. It can form an easy tool for risk stratification of MI.
5. An elevated on admission NLR >3.75 is associated with development of left ventricular systolic dysfunction in patients with acuteSTEMI.

6. A high admission NLR can be utilized for additional risk stratification of the patient so that these patients watched for subsequent development of complications of acuteSTEMI.
7. NLR is a simple and inexpensive tool which can be a novel biomarker for inflammation.
8. Inflammation might be an important causative factor for development of complications in patients with acuteSTEMI.
9. Neutrophilia, Lymphopenia and a high NLR is inversely proportional to the ejection fraction following a STEMI, and would mean a poor left ventricular systolicfunction.
10. Diabetes and hypertension does not independently cause fragmentation ofQRS
11. Combined use of NLR and fQRS in a risk stratification tool might help identifying patients prone for severe left ventriculardysfunction.

LIMITATIONS OF THE STUDY

The study involved only patients with STEMI. Patients with Unstable angina and NSTEMI were not included. The role of inflammation and presence of fQRS in this population also have to be studied. Biomarkers of myonecrosis were not used in the analysis as it was not available for all patients as it was not feasible to do it for all cases. Also we have included only the patients who underwent thrombolysis as a treatment for STEMI.

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Dr. Balaji Thenrajan. "Relationship Between Neutrophil To Lymphocyte Ratio(NLR) And Fragmented QRS Inacute STEMI Patients Treated With Thrombolysis.." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 8, 2019, pp 41-58.