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Original Research Article

Neutrophil-to-lymphocyte ratio (NLR) in the acute coronary syndrome patients presenting in the pre and post-COVID-19 era

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Abstract

Background: The inflammatory pathways play a key role in the pathogenesis of acute coronary syndrome and the severe forms of COVID-19 disease. Thus inflammation may play an interrelation between these two critical situations.
Materials and Methods: In this study, the records of the patients of ACS admitted to the coronary care unit, were analyzed retrospectively. The two groups had 200 patients each. The group-A was randomly taken from the pre-COVID period of July to December 2019 while group-B patients were taken from the COVID/post-COVID period of July 2021 to December 2021. The two groups were compared for the severity of inflammation, through the leukocyte ratios of NLR and d-NLR.
Results: The neutrophil percentage as well as the ANC were significantly higher, while the percentage of lymphocytes and ALC were significantly lower in the group-B patients compared to the group-A patients ($p < 0.05$). The NLR (mean ±SD) was significantly higher in group-B compared to group-A patients (6.38±4.84 vs 5.34±4.37, $p < 0.05$), while the d-NLR showed no significant difference. The NLR values were significantly higher in group-B compared to group-A, for patients of age < 45 years (7.13±5.8 vs 4.3±2.73, $p < 0.05$) and for patients presenting with ST-Elevation ACS (7.17±5.2 vs 5.54±4.22, $p < 0.005$).
Conclusion: The degree of inflammation as indirectly measured by the ratios of NLR and d-NLR, was found to be higher in the ACS patients presenting in the COVID/post-COVID era when compared to those in the pre-COVID era.

Keywords: COVID-19, Neutrophil percentage, Lymphocyte percentage

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1. Introduction

The inflammatory pathways play a key role in the pathogenesis of acute coronary syndrome and the severe forms of COVID-19 disease.[1-5] Thus inflammation may play an interrelation between these two critical situations. The COVID-19 patients have a picture of chronic inflammation and immune dysregulation which can have a triggering effect on endothelial dysfunction. Patients having predisposing conditions for endothelial dysfunction such as diabetes, obesity or prior cardiovascular disease, thus can have worse clinical outcomes, especially in the setting of COVID-19 disease.[6] The neutrophil to lymphocyte ratio (NLR), and derived-Neutrophil to lymphocyte ratio (d-NLR) have been found to be associated with severity and mortality in patients of both ACS and severe COVID-19 disease.[7-9] The Neutrophils to lymphocyte ratio is a readily available and cost-effective indirect measure of inflammation in these situations.

Thus through this study, we hypothesized whether there is a chronic persistent inflammation in the patients in post-COVID era or not. We intended to see for difference in the degree of inflammation, if any in the patients presenting specifically with ACS during pre-COVID and the post-COVID era. NLR and d-NLR were utilized in these patients, as an indirect measure for the presence of inflammation as well as the degree of inflammation.

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2. Materials and Methods

In this study, the records of the patients of ACS admitted to the coronary care unit (CCU) of a tertiary care centre in northern India, were analyzed retrospectively. The two groups had 200 patients each. Group-A was randomly taken from the pre-COVID period of July to December 2019 while group-B patients were taken from the COVID/post-COVID period of July 2021 to December 2021 when the second wave of COVID-19 was settling in India. The Absolute Neutrophil count (ANC), and Absolute Leukocyte Counts (ALC) were obtained from the Total leukocyte count (TLC) and then the NLR (ANC/ALC) and d-NLR (ANC/TLC-ANC) were calculated. The two groups were compared for the severity of inflammation, through these leukocyte ratios of NLR and d-NLR. A subgroup analysis was also done for the mean NLR and mean d-NLR, in relation to the age groups (whether age ≤ 45 years or > 45 years), Gender (Males/females) and the diagnosis at the time of presentation (whether STE-ACS or NSTE-ACS).[**Figure 1**]

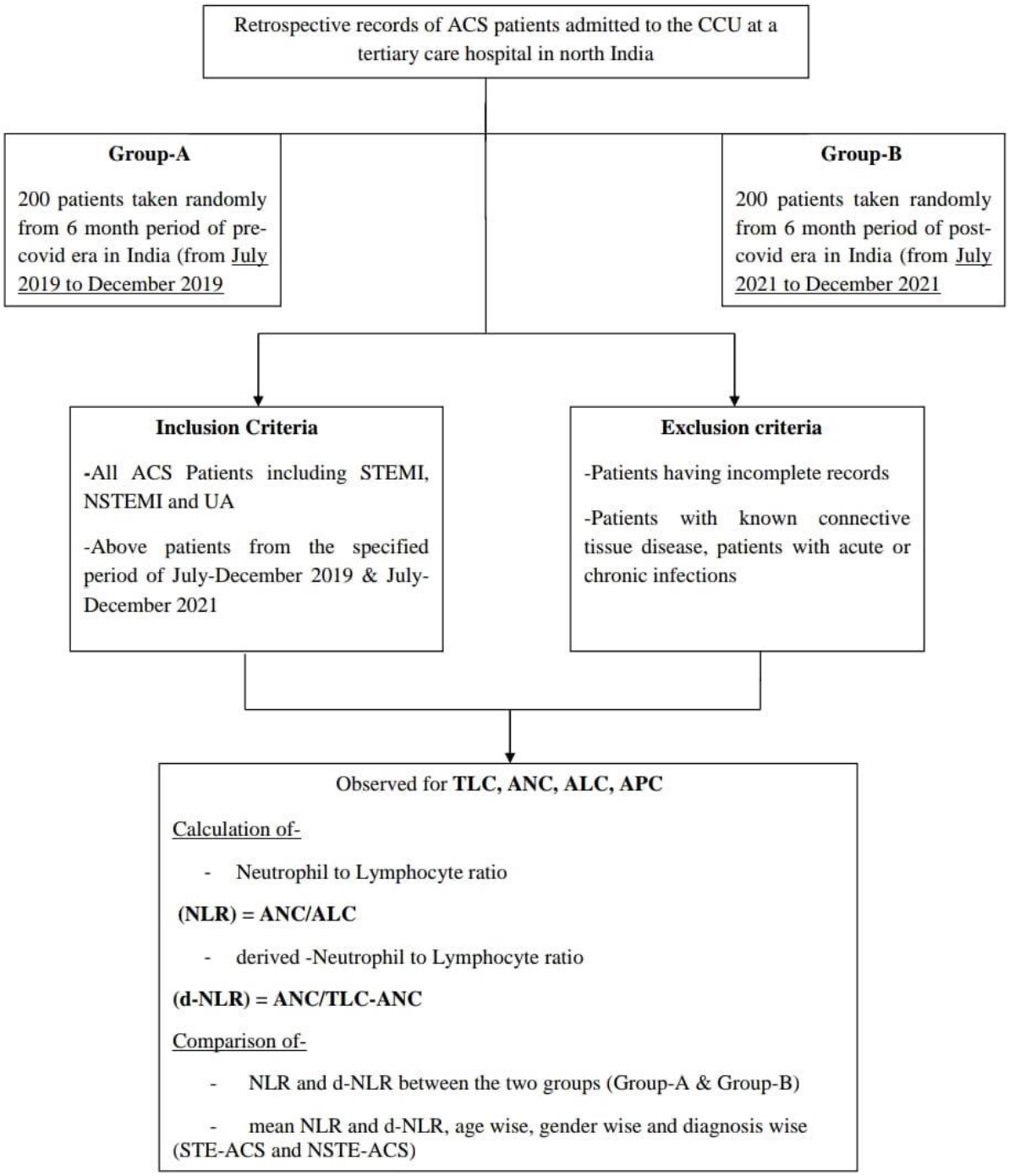

Figure 1: Flowchart showing methodology of the study

2.1. Statistical methods

Frequency distribution, students t-test and pearson chi-square test were used to compare the variables for significant difference between the two groups. Statistical analysis was performed using IBM SPSS Statistics, version 26. Two sided value of $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

On baseline comparison, the patients in both groups were comparable in terms of age, risk factors for coronary artery disease and the diagnosis at the time of presentation (whether STE-ACS or NSTE-ACS) [**Table 1**].

The mean age of presentation was 56±12.55 years in group-A and 55.70±12.43 years in group-B. The male population was significantly higher and the female population significantly lower in group-B (males 84%, females 16%) compared to group-A (males 73%, females 27%). The neutrophils both in terms of percentage count as well as the absolute counts/ANC, were significantly higher in group B [76.35(%) ± 10.93 (%), ANC 9157.20 ± 4091.35] compared to group –A [73.94 (%) ± 11.09 (%), ANC 9157.20 ± 4091.35] ($p < 0.05$). On the other hand, the lymphocytes, both in terms of percentage counts and absolute counts/ALC, were significantly lower in group-B [17.42 (%) ± 9.06 (%), ALC 1872.57 ± 913.97] patients compared to the group-A patients [19.97 (%) ± 9.44 (%), ALC 2100.46 ± 1107.08] ($p < 0.05$) [**Table 1**]. The platelet count was comparable between the two groups.

3.2. NLR and d-NLR

The NLR (mean ±SD) was significantly higher in group-B compared to group-A patients (6.38±4.84 vs 5.34±4.37, $p < 0.05$), while the d-NLR showed no significant difference (**Table 2**).

The NLR values were significantly higher in group-B compared to group-A, for patients of age < 45 years (7.13±5.8 vs 4.3±2.73, $p < 0.05$) and for patients presenting with ST-Elevation ACS (7.17±5.2 vs 5.54±4.22, $p < 0.005$). The NLR values were also significantly higher in group-B compared to group-A, for the male gender (6.49±5.01 vs 5.2±4.15, $p < 0.05$) while females in both the groups did not show any significant difference between them. The mean NLR did not show any significant difference between the two groups when compared in patients of age more than 45 years and in patients presenting with NSTE-ACS (**Table 3**).

Table 1: Baseline characteristics of the study population

Variables	Group-A [Mean± SD, Frequency (%)]	Group-B [Mean± SD, Frequency (%)]	p-value
Age	56.81 ± 12.55	55.70 ± 12.43	.375
Males	73.0%	84.0%	**0.07**
Females	27.0%	16.0%	
CAD	13.5%	18.5%	.173
HTN	20.5%	15.5%	.193
DM	12%	10%	.635
Smoking	48.1%	51.9%	.423
Alcoholic	21.5%	24%	.551
STE-ACS	73.5%	69%	.320
NSTE-ACS	26.5%	31%	.320
Hemoglobin	13.19 ± 2.10	12.97 ± 2.10	.281
TLC	10994.50 ± 3441.83	11739.05 ± 4239.58	**.055**
Neutrophils (N)	73.94 ± 11.09	76.35 ± 10.93	**.030**
Lymphocytes (L)	19.97 ± 9.44	17.42 ± 9.06	**.006**
ANC	8240.92 ± 3143.44	9157.20 ± 4091.35	**.012**
ALC	2100.46 ± 1107.08	1872.57 ± 913.97	**.025**
Platelets	3.42 ± 11.38	2.09 ± 0.722	.101
B.Sugar	132.90 ± 58.14	130.66 ± 55.30	.693

Table 2: Mean NLR and d-NLR values between Group-A and Group-B

Variables	Group-A (Mean± SD)	Group-B (Mean± SD)	p-value
N/L Ratio	5.34 ± 4.37	6.38 ± 4.84	**.024**
derived N/L Ratio	4.43 ± 10.32	4.31 ± 2.82	.872

Table 3: Subgroup analysis for the mean NLR values between Group-A and Group-B patients

Parameters	Mean NLR (Group-A)	Mean NLR (Group-B)	p-value
Age ≤ 45 years	4.3±2.73	7.13±5.79	.016
Age > 45 years	5.52±4.58	6.19±4.57	.185
Males	5.2±4.15	6.49±5.01	.015
Females	5.69±4.92	5.81±3.92	.908
STE ACS	5.54±4.22	7.17±5.19	.004
NSTE ACS	4.77±4.74	4.62±3.39	.844

Table 4: Subgroup analysis for the mean derived-NLR values between Group-A and Group-B patients

Parameters	Mean d-NLR Group-A	Mean d-NLR Group-B	p-value
Age ≤ 45 years	3.2±1.78	4.87±3.42	**.018**
Age > 45 years	4.65±11.16	4.17±2.63	.595
Males	4.57±11.95	4.33±2.89	.802
Females	4.06±2.92	4.21±2.45	.816
STE-ACS	4.77±11.91	4.82±2.99	.962
NSTE-ACS	3.49±2.81	3.17±1.99	.481

The mean d-NLR values were significantly higher in group-B compared to group-A, for patients of age < 45 years (4.87±3.42 vs 3.2±1.78, p < 0.05) [**Table 4**].

5. Discussion

The major findings in the study include higher values of NLR in patients of ACS who presented in the post-COVID period or the period when the second wave of COVID-19 was settling in India from July to December 2021. This was especially found in the younger male population in the post-COVID era. So indirectly it can be said that higher inflammation level was observed in ACS patients presenting in the post-COVID period compared to the pre-COVID period. Chronic inflammation is usually associated with CVD and, the role of inflammation in triggering the plaque vulnerabilization leading to acute coronary event, is also well known.[10,11] ACS is usually caused by the rupture of the atheromatous plaque after a long evolution of a chronic coronary syndrome, which may be associated with persistent and chronic inflammation. A persistently increased systemic inflammation has been associated with a higher risk of atheromatous plaque initiation and progression, The conditions such as periodontal disease or alteration in gut microbiota, have been demonstrated to have persistently increased systemic inflammation as well the associated higher risk of atheromatous plaque initiation and progression.[12,13]

In the present study, male patients of ACS presenting in the post-COVID period, had significantly higher NLR values compared to females specifically in the younger males (< 45 years of age) compared to older age groups. Song BY et al, while studying gender differences in the correlations between immune cells and organ damage indexes in ACS patients, found that the WBCs, Neutrophils, NLR, and MLR, were significantly higher in male patients compared to female patients.[14] Lau ES et al, while studying the gender differences in the inflammatory markers in the hospitalized patients of COVID-19 infection, observed that the male patients had a stronger activation of inflammation as evidenced by higher initial and peak inflammatory markers, as well as worse clinical outcomes.[15] Previous studies in the patients of AMI (Acute myocardial infarction), in contrast, showed that the NLR was considerably higher in older AMI patients compared to the younger counterparts (<60 years).[16,17] Li J et al, in their study in a healthy population, found that older people possessed relatively high NLR.[18]

The patients of STE-ACS in the post-COVID group, in the present study had a significantly higher NLR value when compared to patients of STE-ACS in the pre-COVID group. On the other hand, patients having NSTEMI as a diagnosis, at the time of presentation had no significant difference in the mean-NLR or d-NLR values between the two groups. These findings of our study are also supported by the previous studies in which STEMI patients exhibited a higher inflammatory burden than NSTEMI patients. In the study by Bajari R et al, higher mean NLR was found in STEMI patients compared to the patients with NSTEMI/UA.[17] Similarly, Tohto E et al, observed higher mean NLR values in AMI patients compared to UA patients.[19] Systemic inflammatory burden predisposes individuals for the development of myocardial infarction. Weber B et al in the Partners YOUNG-MI registry found that of individuals who experienced myocardial infarction at a young age, approximately 2.5% had evidence of a systemic inflammatory disease at or before their myocardial infarction.[20] Patients with preexisting atherosclerotic lesions and chronic inflammation, then infected with COVID-19, may be predisposed to a higher risk of disease severity, complications such as acute coronary syndrome (ACS), and mortality, and may present conduction abnormalities, atrial fibrillation, hypotension, left ventricular dysfunction, and elevation in brain natriuretic peptide (BNP) and cardiac troponins.[21-23] In our study higher NLR and d-NLR values indirectly suggested the presence of a higher degree of inflammation in the COVID/post-COVID period.

The history for covid infection whether symptomatic or asymptomatic was not available in the retrospective records. Similarly, the vaccination history was also not available in the records, hence it cannot be hypothesized that the increased degree of inflammation observed in the post-COVID period was because of the effect of COVID-19 vaccination. Secondly, COVID-19 vaccination has not been observed to be associated with increased inflammation.[24,25] There was observed no inflammation at 21 to 31 days post-vaccination with the Pfizer-BioNTech COVID-19 vaccine based on the hematological parameters of neutrophil to lymphocyte ratio, and it was regardless of age and gender.[24] In a study by Pramana KA et al, total lymphocyte count in severe vaccinated COVID-19 patients was higher than in non-vaccinated patients with severe COVID-19 disease, while neutrophil-lymphocyte ratio and CRP were lower in vaccinated subjects.[25] Similarly in another study by Zhu X et al, a short-term and long-term reduction in inflammation was observed in fully vaccinated participants compared to unvaccinated participants, which could in part explain the reduced disease severity and mortality in vaccinated individuals.[26]

A few studies have highlighted the surge in the incidence of acute myocardial infarction during the COVID pandemic period especially in younger individuals.[27,28] The key finding in our study is the increased degree of inflammation (through NLR and d-NLR) in the younger patients of ACS presenting in the post-pandemic period., thus warranting the need for further larger, prospective cohort studies into this matter.

6. Conclusion

The degree of inflammation as indirectly measured by the ratios of NLR and d-NLR, was found to be higher in the acute coronary syndrome patients especially the younger males,

presenting in the COVID/post-COVID era when compared to those in the pre-COVID era.

4. Source of Funding

None.

5. Conflict of Interest

None.

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