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Original Article

Neutrophil to lymphocyte ratio as a predictor of myocardial damage and cardiac dysfunction in acute coronary syndrome patients

Chen Chen, Bai Lin Cong, Min Wang, Muhammad Abdullah, Xiao Long Wang, Yin Hua Zhang, Shun Ji Xu, Lan Cui**

Department of Cardiology, Yanbian University Hospital, Yanji, China

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ABSTRACT

Background: Neutrophil to lymphocyte ratio (NLR) in peripheral blood is established to correlate with the morbidity and mortality of heart disease patients. We aimed to define the severity of inflammation (NLR) by observing the association of NLR with cardiac functions or myocardial damage parameters in patients with acute myocardial infarction.

Methods: Data from 715 patients who underwent percutaneous coronary intervention (PCI) within 72 hours of incidence in 2016 were analysed retrospectively.

Results: The NLR ranges from 0.50 to 46 (medium ± SD, 2.76 ± 2.96) in 715 patients. NLR positively correlated with myocardial damage (NLR vs. CK-mB: $p < 0.0001$) but negatively correlated with myocardial function (NLR vs. EF: $p < 0.0001$; NLR vs. FS: $p < 0.0001$). Myocardial damage markers (CK, CK-mB, ASL, LDH) were significantly increased, and cardiac contractile parameters (EF and FS) were reduced at NLR > 2.76 compared to those of NLR < 2.76. ELISA analysis has shown that IL-10 was significantly increased when NLR ≥ 4.6 and TGF-β was increased at NLR > 4. The correlation was diminished between NLR and CK-mB at NLR > 2.76 or at NLR > 4, but that of NLR and EF or FS was maintained in NLR > 2.76 and at NLR > 4. EF and FS were comparable between NLR > 2.76 and NLR > 4. But myocardial damage parameters increased significantly at NLR > 4 compared to those of NLR > 2.76.

Conclusion: NLR is a strong predictor of myocardial damage in acute myocardial patients. High NLR are associated with myocardial dysfunction in all the patients. Severe inflammation (NLR) can predict the consequence of the heart in patients with coronary syndrome.

* *Corresponding authors*. Department of Cardiology, Yanbian University Hospital, Yanji City 133000, Jilin Province, China (L. Cui). Department of Clinical Laboratory, Yanbian University Hospital, Yanji City 133000, Jilin Province, China (S.J.Xu).

E-mail address: lancui@ybu.edu.cn (L. Cui).

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1. Introduction

Cardiovascular diseases are the number one causes of mortality in humans worldwide, and coronary syndrome (myocardial infarction, MI) is one of the prevalent conditions those are responsible for fatal heart attack and heart failure.[1] Impaired vascular perfusion in MI and reperfusion cause the damage of the myocardium, depending on the duration of ischaemia and metabolic demand of the tissue. As a consequence, systematic and local inflammation can be triggered, which is important in the remodelling and the scar formation of the myocardium.[2–4]

There are two main phases of inflammation during MI: the inflammatory phase and the proliferative phase. Neutrophils are the first leukocytes to be found in damaged area. Their activation produces large amounts of inflammatory mediators those regulate the response to tissue injury, demonstrating hypoxic damage, proteolytic enzymes and other mediators.[4–6] At the infarct site, neutrophils release free radicals which act as an injury pathway for cardiomyocytes. The release of proteo-enzymes helps the clearance of the infarct and also amplifies immune cell recruitment (in particular M1 macrophage). As such, neutrophils are involved in not only inducing macrophage to the infarct site, but also allowing the clearance of debris.[7–10]

In contrast, lymphocytes play vital roles in the remodelling of the myocardium following inflammation. For example, CD4+ T regulatory cells constitute a particular anti-inflammatory immune regulatory lymphocyte subset which is generated in the thymus and highly enriched for T cells with autoantigen specificity.[11] T cells are essential for the recruitment of proangiogenic macrophages and collateral artery formation.[11–13] B cells are involved in monocyte recruitment through the CCL7 pathway.[2,11–14] The clearance of debris, activation of fibroblasts and collagen deposition for scar formation and neovascularisation (the proliferative phase) occur 3–4 days after MI.[8,14,15] The release of inflammatory and anti-inflammatory mediators (IL-10, TGF-β and pro-resolving mediators, [8,14,16]) from neutrophil or lymphocyte cells promotes neutrophil apoptosis and phagocytic uptake by macrophages.[9,10,15] IL-10 secreted by T lymphocytes inhibits the production of inflammatory cytokines, stabilises the matrix and regulates ECM metabolism. Macrophages engulfing apoptotic neutrophils are a key activator of the anti-inflammatory response and potent inhibitor of pro-inflammatory cytokines.

Neutrophils are seen as a marker of ongoing inflammation and lymphocytes as a marker of regulatory pathways. Neutrophil-to-lymphocyte ratio (NLR) (calculated via dividing neutrophil count by lymphocyte count) as an indication of systemic inflammation has been demonstrated to be associated with poor clinical outcomes in various cardiovascular diseases, including acute coronary syndrome. Recent accumulating evidence points that high NLR to be independently and strongly associated with increased risk of complications and mortality post-acute MI.[5,17–24] Here, our aim is to evaluate the level of NLR that is associated with myocardial dysfunction (EF and FS from echocardiography) or damage (CK-mB) in 715 myocardial infarction patients. NLR is readily available, so it may be used as a cost-effective adverse predictor.[5,21]

2. Methods

2.1. Patients

Data from 1111 patients who underwent PCI 72 hours after the onset at Yanbian University Affiliated Hospital, Jilin province in China (from January 2015 to December 2016) were analysed retrospectively. We excluded 396 patients who had inflammatory diseases such as gastritis, chronic cholecystitis, nephritis, rhinitis, pharyngitis, bronchitis, myocarditis, rheumatoid arthritis, gout, immune system disorders and cancer in analysis group, and the count of cohort in the study was 715. Basic demographics, history, diagnosis at presentation, blood pressure, weight, complete blood count and echocardiogram results were obtained. The study was approved by the Ethical Committee of Yanbian University Hospital with the informed consent to the patients.

2.2. Statistical analysis

All analyses were performed using SPSS 23. The main parameters tested were: "NLR ratio" as the independent variables. The dependent variables were "EF", "FS" and "CK-mB". Pearson's correlation was performed, and correlation and p values were obtained to assess the strength of any association between variables. The descriptive statistics (on SPSS 23) was used for details on the overall data and the parameters were expressed as means ± SD. Firstly we analysed all the patients together. Next, we divided each of the groups into high NLR and low NLR. CK-mB in different NLR groups was expressed as means ± SE. The cut-off NLR value was 2.76, which was the median value of 715 patients. Student unpaired t-test (followed by Bonferroni correction) was used for testing the significance of the parameters between groups. Scatter plot graphs were used to demonstrate visually whether there are any relationships. $p < 0.05$ was considered significant.

2.3. Detection of inflammatory and anti-inflammatory cytokines from arterial blood samples

Blood samples were drawn from the coronary artery before PCI procedure. The IL-10 and TGF-β concentration in the plasma was measured by using an enzyme-linked immunosorbent assay (ELISA).

3. Results

A total of 715 patients with myocardial infarction who underwent PCI with stent within 72 hours of symptom onset were enrolled in our study. The mean age was 61.38 (±9.84) years, and 417 (58.32%) of the patients were men. The baseline clinical characteristics of myocardial function (e.g., EF, FS and SV) and myocardial damage (e.g., LDH, CK, CK-mB, AST) were shown in Table 1. The mean NLR of cohort was 2.76 ± 2.96.

In all the patient groups, there was a positive linear regression of NLR versus CK-mB ($r = 0.264$, $p < 0.0001$), negative linear regression of NLR versus EF ($r = -0.208$, $p < 0.0001$) or FS

Table 1 – Descriptive Statistical Analysis of Patients with Acute Myocardial Infarction

Variable	Total	
	Mean ($n=715$)	SD
NLR	2.7607	2.95855
Age	61.3776	9.83534
BMI	25.0484	4.10604
WBC (4–10) × 10^9/L	7.6625	2.64445
HGB (110–160) g/L	136.7636	16.75549
PLT (100–300) × 10^9/L	214.4517	55.79184
NEU# (2–7.7) × 10^9/L	4.7862	2.44535
LYM# (0.8–4) × 10^9/L	2.1317	0.81169
MON# (0.12–0.8) × 10^9/L	0.5759	0.25681
EOS# (0–0.5) × 10^9/L	0.1467	0.16398
BAS# (0–0.1) × 10^9/L	0.0235	0.03995
LDH (115–220) IU/L	248.9188	207.99504
CK (25–196) IU/L	283.3113	649.86892
CK-MB (0–25) IU/L	31.4671	57.60045
AST (0–40) U/L	43.0198	69.86126
ALT (0–40) U/L	40.5114	366.73486
CREA (75–115) μmol/L	74.1738	23.83924
EF (57–75) %	59.5273	6.34161
FS (20–40) %	29.5972	5.08086
SV (60–120) mL	71.0386	8.86597
CO (3.5–8.0) L/min	4.9013	0.70446
E/A	1.0119	0.41200
DT ms	210.1832	46.03374

Table 2 – Correlation Between N/L Ratio and Laboratory Characteristics

Variable	Total	
	r	p
Age	0.050	0.184
BMI	0.214	0.000
WBC (4–10) × 10^9/L	0.479	0.000
HGB (110–160) g/L	0.083	0.027
PLT (100–300) × 10^9/L	−0.031	0.410
NEU# (2–7.7) × 10^9/L	0.670	0.000
LYM# (0.8–4) × 10^9/L	−0.458	0.000
MON# (0.12–0.8) × 10^9/L	0.133	0.000
EOS# (0–0.5) × 10^9/L	−0.198	0.000
BAS# (0–0.1) × 10^9/L	−0.008	0.836
LDH (115–220) IU/L	0.312	0.000
CK (25–196) IU/L	0.285	0.000
CK-MB (0–25) IU/L	0.264	0.000
AST (0–40) U/L	0.269	0.000
ALT (0–40) U/L	0.010	0.785
CREA (75–115) μmol/L	0.126	0.001
EF (57–75) %	−0.208	0.000
FS (20–40) %	−0.225	0.000
SV (60–120) mL	−0.086	0.021
CO (3.5–8.0) L/min	−0.034	0.362
E/A	0.030	0.427
DT ms	−0.015	0.679

($r=-0.225$, $p<0.0001$) (Table 2). The results suggest that the associations of NLR with these parameters were statistically significant (Fig. 1A–C).

The patients were divided into low NLR (<2.76, $n=522$) and high NLR (>2.76, $n=193$) groups. The parameters of cardiac functions and myocardial damage of respective groups were presented in Table 3. EF and FS were not significantly different between NLR low and high groups. LDH, CK, CK-mB and AST, however, were significantly higher in NLR > 2.76 group compared to those of NLR < 2.76 (Table 3). Furthermore, we have noticed that ALT and creatinine were also significantly increased in NLR > 2.76 group (Table 3).

In NLR < 2.76 group, NLR positively correlates with CK-mB ($r=0.143$, $p=0.001$) and negatively associates with EF ($r=-0.131$, $p=0.003$) or with FS ($r=-0.102$, $p=0.020$). Therefore, the associations between NLR and myocardial function were preserved in this patients group (Table 4).

In NLR > 2.76 group, the association between NLR and CK-mB was absent ($r=0.083$, $p=0.253$). The correlation between NLR and EF was reduced (NLR vs. EF: $r=-0.128$, $p=0.07$) but still significant between NLR and FS (NLR vs. FS: $r=-0.228$, $p=0.001$) (Table 4).

It is possible that high NLR (i.e., greater systemic inflammation) and greater damage of myocardium triggered the remodelling and recovering process, which obscures the adverse effects on myocardial function. Anti-inflammatory cytokines (e.g., IL-10 or TGF-β) are known to be induced following inflammation after myocardial infarction, which plays fundamental roles in the proliferative process following MI.

Therefore, we detected IL-10 and TGF-β in the coronary arterial blood samples of the patients and compared between NLR > 2.76 and NLR < 2.76 groups. Results show that IL-10 or TGF-β were not different between NLR > 2.76 and NLR < 2.76 (data not shown). Instead, IL-10 became significantly higher

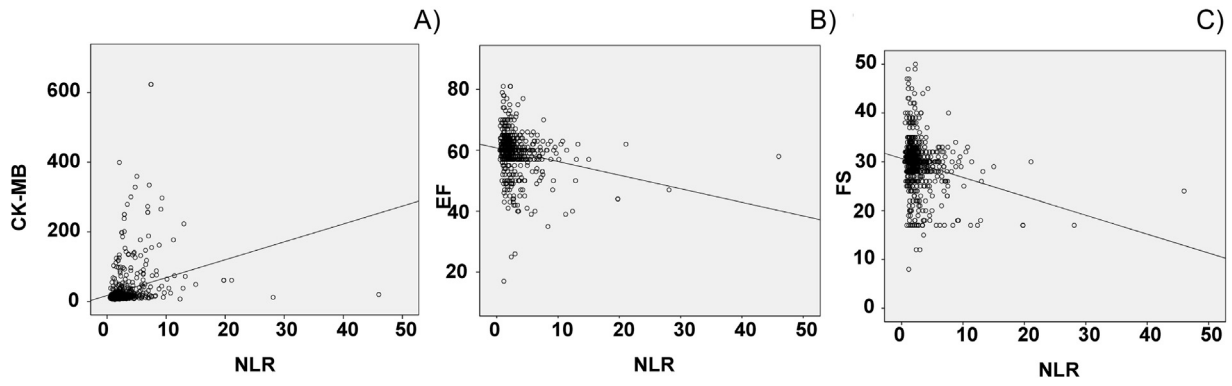

Fig. 1 – Correlation of neutrophil-to-lymphocyte ratio (NLR) with CK-mB (A), EF (B) and FS (C). Pearson rank correlation was used to evaluate the relation between NLR and other parameters.

Table 3 – Descriptive Statistical Analysis of Low NLR and High NLR

Variable	NLR < 2.76, $n = 522$		NLR > 2.76, $n = 193$		p
	Mean	SD	Mean	SD	
NLR	1.6911	0.53428	5.6535	4.50038	
Age	61.5000	9.46237	61.0466	10.79896	0.607
BMI	24.9787	3.83970	25.2368	4.75827	0.456
WBC (4–10) × 10^9/L	6.9209	2.02447	9.6683	3.05693	0.000
HGB (110–160) g/L	136.2395	15.97581	138.1813	18.67327	0.169
PLT (100–300) × 10^9/L	215.2701	54.98789	212.2383	57.99888	0.519
NEU# (2–7.7) × 10^9/L	3.8253	1.35848	7.3851	2.81596	0.000
LYM# (0.8–4) × 10^9/L	2.3639	0.78704	1.5036	0.47554	0.000
MON# (0.12–0.8) × 10^9/L	0.5388	0.20971	0.6764	0.33470	0.000
EOS# (0–0.5) × 10^9/L	0.1676	0.16565	0.0902	0.14539	0.000
BAS# (0–0.1) × 10^9/L	0.0231	0.01557	0.0245	0.07260	0.764
LDH (115–220) IU/L	201.4568	110.21854	377.0415	324.25343	0.000
CK (25–196) IU/L	144.8393	309.54999	657.1140	1056.56799	0.000
CK-MB (0–25) IU/L	19.7414	27.09584	63.1813	94.66274	0.000
AST (0–40) U/L	28.1667	33.79825	83.3579	113.37827	0.000
ALT (0–40) U/L	24.4588	24.26591	83.6000	702.33071	0.247
CREA (75–115) μmol/L	72.3255	19.59934	79.1905	32.22256	0.006
EF (57–75) %	60.3851	5.73898	57.2073	7.26425	0.000
FS (20–40) %	30.1877	4.84493	28.0000	5.36579	0.000
SV (60–120) mL	71.4253	8.58150	69.9927	9.53818	0.055
CO (3.5–8.0) L/min	4.9060	0.67550	4.8886	0.77914	0.784
E/A	0.9816	0.35007	1.0937	0.53802	0.008
DT ms	213.0460	44.45652	202.4404	49.34454	0.006

Table 4 – Correlation Between N/L Ratio and Laboratory Characteristics

Variable	NLR < 2.76, $n = 522$		NLR > 2.76, $n = 193$	
	r	p	r	p
Age	−0.002	0.967	0.138	0.055
BMI	−0.057	0.193	0.431	0.000
WBC (4–10) × 10^9/L	0.252	0.000	0.379	0.000
HGB (110–160) g/L	0.130	0.003	0.079	0.277
PLT (100–300) × 10^9/L	−0.001	0.989	−0.039	0.594
NEU# (2–7.7) × 10^9/L	0.586	0.000	0.515	0.000
LYM# (0.8–4) × 10^9/L	0.410	0.000	−0.524	0.000
MON# (0.12–0.8) × 10^9/L	0.170	0.000	−0.051	0.428
EOS# (0–0.5) × 10^9/L	0.002	0.966	−0.204	0.005
BAS# (0–0.1) × 10^9/L	0.000	0.994	−0.024	0.743
LDH (115–220) IU/L	0.221	0.000	0.115	0.110
CK (25–196) IU/L	0.113	0.010	0.105	0.148
CK-MB (0–25) IU/L	0.143	0.001	0.083	0.253
AST (0–40) U/L	0.082	0.064	0.082	0.258
ALT (0–40) U/L	0.003	0.938	−0.041	0.572
CREA (75–115) μmol/L	0.217	0.000	0.048	0.513
EF (57–75) %	−0.131	0.003	−0.128	0.076
FS (20–40) %	−0.102	0.020	−0.228	0.001
SV (60–120) mL	0.004	0.930	−0.101	0.164
CO (3.5–8.0) L/min	−0.007	0.869	−0.059	0.414
E/A	−0.068	0.120	−0.065	0.372
DT ms	0.047	0.282	0.090	0.214

when NLR > 4.6 ($p = 0.05$, $n = 24$ vs. $n = 18$). Similarly, TGF-β became greater when NLR > 4 ($p = 0.05$, $n = 27$, $n = 20$) (Fig. 2).

When the patients were divided into NLR > 4 and NLR < 4 groups, the parameters of myocardial damage (LDH, CK, CK-mB, AST) were increased even further, and the concentrations were significantly greater than that of NLR > 2.76 (CK-mB; some examples were shown in Fig. 3 and Table 5). EF and FS were comparable between NLR > 2.76 and NLR > 4 groups (Fig. 3 and Table 5), but were significantly greater than all patients' data. In NLR > 4 group, the association between NLR and CK-mB was absent ($r = 0.024$, $p = 0.79$, Table 6). However, NLR negatively associates with EF ($r = -0.19$, $p = 0.045$) or with FS ($r = -0.3$, $p = 0.001$) in NLR > 4 group. Therefore, the association between NLR and myocardial function was preserved in all patients' group (Table 6).

These results confirm that high NLR is strongly associated with the extent of myocardial damage. Inflammatory and anti-inflammatory cytokines are significantly increased when NLR is larger than 4. The correlation between myocardial function and NLR was preserved in all patient groups.

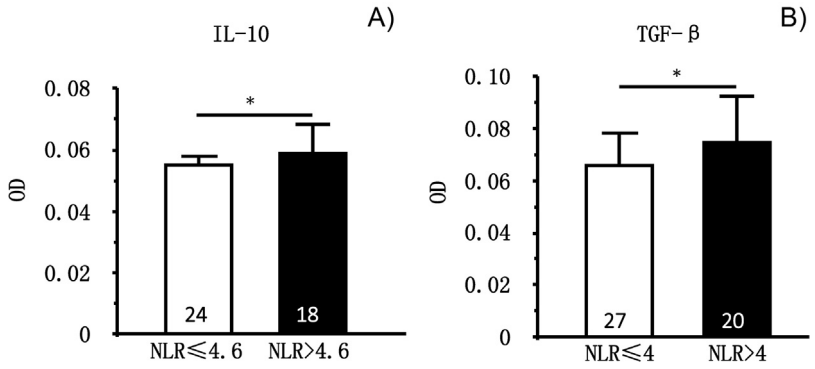

Fig. 2 – Plasma level of IL-10 and TGF-**β** in ACS patients at two levels of NLR. (A) IL-10 was significantly increased when NLR > 4.6 ($p = 0.05$). (B) TGF-b was significantly increased when NLR was >4 ($p = 0.05$).

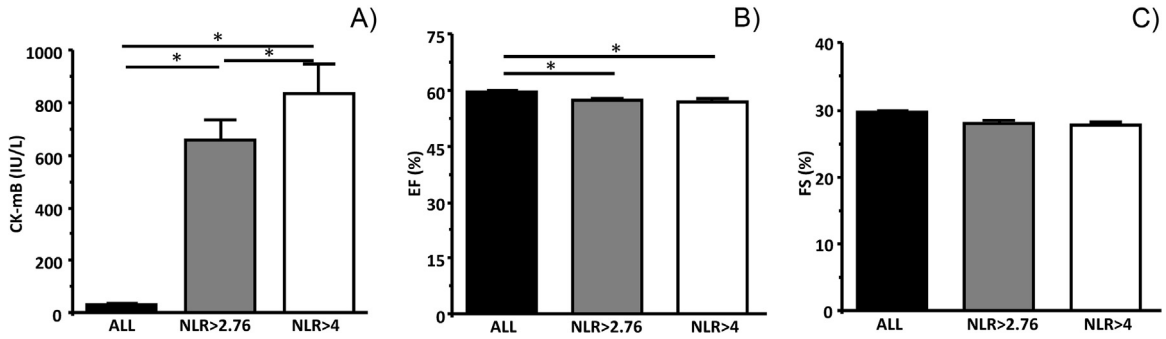

Fig. 3 – Comparison of CK-mB, EF and FS in NLR > 2.76 and NLR > 4 to all patients's data. (A) CK-mB in all patients, NLR > 2.76 and NLR > 4. CK-mB was significantly increased in NLR > 2.76 and in NLR > 4 groups compare to all patients group ($p < 0.001$, $p < 0.001$, $n = 193$, $n = 112$ and $n = 715$, respectively). CK-mB was greater in NLR > 4 compare to that in NLR > 2.76 ($p < 0.003$). (B) EF was significantly lower in NLR > 2.76 and NLR > 4 compare to all patients group ($p < 0.001$ and $p = 0.02$). EF was not different between NLR > 2.76 and NLR > 4 ($p = 0.6$). (C) FS was not different among groups ($p = 0.4$, $p = 0.5$ and $p = 0.2$, respectively).

Table 5 – Descriptive Statistical Analysis of Low NLR and High NLR

Variable	NLR < =4, n=603		NLR > 4, n=112		p
	Mean	SD	Mean	SD	
NLR	1.9094	0.75345	7.3629	5.28372	
Age	61.3858	9.62852	61.3304	10.89044	0.956
BMI	25.0056	3.86506	25.2518	5.22747	0.568
WBC (4–10) × 10^9/L	7.0645	2.05207	10.8734	3.12734	0.000
HGB (110–160) g/L	136.3775	15.93488	138.6250	20.68081	0.286
PLT (100–300) × 10^9/L	214.3808	55.50209	214.7946	57.34064	0.944
NEU# (2–7.7) × 10^9/L	4.0560	1.48568	8.7240	2.81531	0.000
LYM# (0.8–4) × 10^9/L	2.2715	0.78454	1.3692	0.45749	0.000
MON# (0.12–0.8) × 10^9/L	0.5514	0.22043	0.7041	0.37699	0.000
EOS# (0–0.5) × 10^9/L	0.1633	0.16687	0.0738	0.12196	0.000
BAS# (0–0.1) × 10^9/L	0.0231	0.01515	0.0286	0.09627	0.556
LDH (115–220) IU/L	214.2421	129.20217	434.9732	382.02303	0.000
CK (25–196) IU/L	181.5411	431.73023	830.3839	1159.20538	0.000
CK-MB (0–25) IU/L	22.4702	34.28610	79.9375	110.20368	0.000
AST (0–40) U/L	32.4740	45.06857	100.0818	128.72124	0.000
ALT (0–40) U/L	41.5939	399.00941	34.4091	26.19766	0.849
CREA (75–115) μmol/L	72.8111	21.74906	81.1727	32.24387	0.011
EF (57–75) %	59.9719	6.17309	57.1339	6.69475	0.000
FS (20–40) %	29.9487	5.00040	27.6875	5.08846	0.000
SV (60–120) mL	71.1781	9.00913	70.2589	8.00422	0.311
CO (3.5–8.0) L/min	4.8972	0.68790	4.9205	0.78856	0.753
E/A	0.9981	0.38590	1.0972	0.53695	0.059
DT ms	211.4354	45.33791	203.6964	49.20885	0.104

Table 6 – Correlation Between N/L Ratio and Laboratory Characteristics

Variable	NLR < 4, $n = 602$		NLR > 4, $n = 113$	
	r	p	r	p
Age	−0.015	0.712	0.177	0.063
BMI	−0.011	0.789	0.569	0.000
WBC (4–10) × 10^9/L	0.287	0.000	0.242	0.010
HGB (110–160) g/L	0.087	0.032	0.091	0.338
PLT (100–300) × 10^9/L	−0.026	0.542	−0.095	0.319
NEU# (2–7.7) × 10^9/L	0.629	0.000	0.384	0.000
LYM# (0.8–4) × 10^9/L	−0.476	0.000	−0.567	0.000
MON# (0.12–0.8) × 10^9/L	0.201	0.000	−0.124	0.194
EOS# (0–0.5) × 10^9/L	−0.059	0.149	−0.122	0.256
BAS# (0–0.1) × 10^9/L	−0.060	0.144	−0.055	0.570
LDH (115–220) IU/L	0.297	0.000	0.026	0.783
CK (25–196) IU/L	0.205	0.000	0.024	0.799
CK-MB (0–25) IU/L	0.200	0.000	−0.010	0.916
AST (0–40) U/L	0.215	0.000	0.005	0.957
ALT (0–40) U/L	0.065	0.116	0.000	0.996
CREA (75–115) μmol/L	0.166	0.000	0.019	0.843
EF (57–75) %	−0.207	0.000	−0.190	0.045
FS (20–40) %	−0.158	0.000	−0.300	0.001
SV (60–120) mL	−0.054	0.188	−0.198	0.036
CO (3.5–8.0) L/min	−0.033	0.412	−0.114	0.231
E/A	0.041	0.315	−0.098	0.305
DT ms	−0.047	0.253	0.121	0.206

4. Discussion

NLR is an established biomarker for systemic inflammation. Accumulating evidence has demonstrated the strong link between high NLR and increased morbidity and mortality in a wide range of cardiovascular diseases, including acute coronary syndrome.[25–30] In this study, we have analysed the data retrospectively from 715 patients who underwent PCI 72 hours from onset. Our results showed that NLR was strongly associated with myocardial damage (CK-mB) and negatively associated with cardiac contractility (EF and FS). High NLR (either >2.76 or >4) strongly predicts the severity of myocardial damage. The correlations between NLR and myocardial contraction (EF or FS), however, were maintained, suggesting that the extent of inflammation is associated with contractile dysfunction of the heart. We also found that anti-inflammatory cytokines (IL-10 and TGF-β) were significantly increased in high NLR group >4.6 or >4, respectively. It is possible that the anti-inflammatory mechanisms may have prevented the functional deterioration of the myocardium.

Our results are in agreement with previous studies suggesting that elevated leucocyte counts do associate with worse clinical indexes in patients with acute coronary syndromes (ACS).[16] Dogan et al showed that increased neutrophil count positively correlates with increased myocardial damage, evidenced by CK-mB, cardiac troponin and scintigraphic infarct size.[31] Furthermore, previous studies have shown both neutrophilia and lymphocytopenia to be independently and strongly associated with an increased risk of complications and mortality post-AMI.[5,6,17–24] Similar to our study, Horne et al investigated patients with coronary artery disease (CAD) (without MI) to check whether inflammatory markers can help to identify the risk of death/MI. The study followed up over 3000 patients on a long-term basis. Cox regression was used to assess the predictive ability of the WBC, neutrophil, lymphocyte and monocyte counts and NLR. Their study showed that patients in the top quartile had a 2.2-fold increased risk compared to that of the lower quartile.[24]

There have been many studies on the predictive value of NLR for adverse outcome and mortality post-MI. Higher NLR values seem to be more predictive.[18,29,32,33,21,23,34] Shen et al investigated the association of NLR with long-term mortality after STEMI treated with primary PCI. The study tested the hypothesis that in the acute phase of STEMI, whether NLR could be used to predict long-term prognosis. Their results indicate that patients in the highest NLR quartile were 4 times more likely to die during hospitalisation and during long-term follow-up.[35] Arbel et al explored whether NLR provides additive prognostic value in STEMI.[29] Patients undergoing STEMI were put into two groups (high/low NLR), and logistic regression was used to assess in-hospital complications and LVEF based on NLR. The results showed that higher NLR values (>6.5) were associated with lower EF and increased 30 days and 5-year mortality.[29] Oncel et al studied the relationship of NLR with GRACE risk score to in-hospital cardiac events in patients with STEMI.[33] The results showed that GRACE risk score was over 100 when NLR > 2.65 and over 140 when NLR > 6.48 at admission. Therefore, NLR was significantly associated with adverse in-hospital effects, indicating that NLR at this level can be used as a predictor of negative cardiac outcomes.[33] The mean NLR in 715 patients enrolled in our study was 2.76, and myocardial damage (CK-mB) was greater in NLR high group ($p < 0.0001$). The strong association between NLR and CK-mB suggests that the level of inflammation is predictable of the extent of myocardial damage, which may account for the adverse outcome of myocardial functions. At NLR > 2.76, inflammation affected not only heart, but kidney or liver functions also, since ALT and creatinine were also increased significantly. These results indicate that patients with NLR > 2.76 should raise alarm for multiple organ damage. Large cohort from wider range of communities is necessary to set the level of NLR for clinical indications.

Given that NLR is a strong and independent predictor of mortality in patients with coronary syndrome, incorporating echocardiographic measures should aid in the management of the patients under risk. The changes in the systolic and diastolic function and their correlation to NLR may improve the prognostic value of clinical assessment of the risk, which will be important in providing a better understanding of the patients. Our results indicate that NLR is associated with adverse LV function in coronary syndrome patients. When the group of patients were divided into high and low NLR (i.e., larger or lower than medium NLR > 2.76 or <2.76), EF and FS were indeed reduced in high NLR group. In addition, the correlation between NLR and myocardial contraction was maintained throughout NLR group. These results demonstrate that inflammation is associated with myocardial dysfunction.

It is possible that pro-inflammatory cytokines exert negative inotropic effects in cardiac tissue.[36,37] High cytokines levels, such as IL-1, are associated with ventricular diastolic diameter increase and collagen deposition in the infarcted area after several weeks of MI, and as such, IL-1 induces abnormalities in cardiac metabolism and promotes myocardial remodelling leading to heart failure.[36,38,39] Therefore, the

pro-inflammatory cytokines (TNF-α levels, IL-6, etc.) at high NLR may play crucial roles in the development of heart failure. In contrast, anti-inflammatory cytokines are involved in the reparatory process following myocardial infarction. Our results showed that IL-10 and TGF-β were increased in NLR high group (>4.6 or >4), indicating that cytokine production could be the consequence of the level of inflammation following infarction. Recent evidence has shown that IL-10 infusion at day-7 post-MI attenuated inflammation and significantly decreased LV dilation and improved ejection fraction (both $p < 0.05$) following myocardial infarction.[40] Another inflammatory cytokine, TGF-β, is markedly induced and rapidly activated in the infarcted myocardium. Experimental studies suggest that TGF-β signalling may be crucial for repression of inflammatory gene synthesis in healing infarcts mediating resolution of the inflammatory infiltrate. In addition, TGF-β may promote extracellular matrix deposition in the infarct by upregulating collagen and fibronectin synthesis.[41,42] The changes of inflammatory cytokines and their impacts on myocardium following MI and the downstream signalling pathways are needed to study in more detail in order to design safe and effective therapeutic strategies.

There are increased numbers of patients admitted to hospital with cardiovascular diseases each year. It is vital for early diagnosis to prevent deterioration of heart function. The study helps to define inflammation as an important risk factor; NLR level > 2.76 can point to myocardial damage and reduced heart function in these patients. A delayed diagnosis can result in worse prognosis, so an early assessment with easily available NLR may be vital. In our study, we confirm that NLR can be used as a predictor for myocardial damage and cardiac dysfunction. High level of NLR (e.g. >4) is linked with elevated anti-inflammatory cytokines. Comprehensive studies need to be undertaken for better understandings of the inflammatory profiles and their influences during the process of pathology following MI.

Conflict of interest

The authors declare no conflict of interest.

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