Clinical Investigations

Neutrophil to Lymphocyte Ratio as a Predictor of Long-term Mortality in African Americans Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: Neutrophil to lymphocyte ratio (N/L ratio) has been shown to predict long-term mortality in patients undergoing percutaneous coronary intervention (PCI). African Americans have been shown to have lower mean neutrophil counts compared to whites. The usefulness of the N/L ratio in predicting long-term mortality in African Americans undergoing PCI is unknown.

Methods: We evaluated a total of 372 African American patients (327 patients with lower N/L ratio [<3.5] and 45 patients with higher N/L ratio [≥3.5]) who underwent PCI during January 2003 to August 2005. The primary endpoint was all-cause mortality at a median follow-up to 3.6 years.

Results: During the median (± SD) follow-up period of 3.6 ± 1 years, there were a total of 48 deaths. The mortality rate was 10.4% in the group with a lower N/L ratio and 31.1% in the group with a higher N/L ratio (unadjusted p<0.001). After adjustment for covariates with significant impact on mortality, N/L ratio was still a strong and independent predictor of long-term mortality with a hazard ratio (HR) of 2.1 (95% confidence interval [CI]: 1.1–4; p = 0.02). N/L ratio was also found to be a strong and independent predictor of long-term mortality even when analyzed as a categorical variable with 3 groups (HR of 0.39 for lower tertile compared to the upper tertile, 95% CI: 0.19–0.81; p = 0.012) and as a continuous variable (p = 0.002).

Conclusion: N/L ratio is a powerful independent predictor of long-term mortality in African Americans undergoing PCI.

Key words: Neutrophil to lymphocyte ratio, African Americans, Percutaneous coronary intervention

Introduction

Among the total white blood cell count (WBC) and its subtypes, neutrophil to lymphocyte ratio (N/L ratio) has been shown to have the greatest predictive power for death/myocardial infarction (MI) in patients with or at high risk for coronary artery disease (CAD).[1] Also, N/L ratio has been shown to predict long-term mortality in patients admitted with ST-segment elevation myocardial infarction (STEMI)[2] and in patients undergoing percutaneous coronary intervention (PCI).[3]

African Americans have been shown to have lower mean neutrophil counts and similar lymphocyte counts compared to whites.[4] The usefulness of neutrophil to lymphocyte count in predicting long-term mortality in African Americans undergoing PCI is unknown. We sought to study the impact of neutrophil to lymphocyte count on long-term mortality in African Americans undergoing PCI.

Methods

Study Cohort

This is a retrospective analysis of 372 African American patients from our bolus-only platelet glycoprotein IIb/IIIa inhibitor (GPI) database. We retrospectively analyzed 1,293 patients (1,001 consecutive patients during January 2003 to August 2004 and 292 consecutive patients during December 2004 to August 2005 in 2 separate studies)[5,6] who underwent PCI with a GPI bolus-only regimen. In our previous studies, in-hospital outcomes were the primary endpoints and patients undergoing repeat procedures in different hospital admissions during the study period were included. Because long-term mortality is the endpoint in the current study, only the first PCI of a patient occurring during this time period was included. Patients without a valid social security number were excluded from the study because longer term follow-up was obtained using the Social Security Death Index. From this database we included all African Americans who had a differential WBC count measured prior to the PCI in the current study. The University Hospital of Brooklyn's Institutional Review Board approved the study. Demographic, periprocedural, and laboratory data were collected by reviewing charts and hospital records. The in-hospital events and the length of stay were also recorded. Patients with STEMI were not treated with a bolus-only GPI and therefore were excluded from the database.

Clin. Cardiol. 32, 12, E6–E10 (2009)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20503

Received: May 17, 2008
Accepted with revision: June 24, 2008

Periprocedural Medication

All patients were loaded with aspirin (325 mg) and clopidogrel (300–600 mg) prior to PCI. All patients received an initial bolus of intravenous 40 units/kg unfractionated heparin (UFH) plus a bolus of GPI (0.25 mg/kg abciximab, 25 μg/kg tirofiban or 180 μg/kg ×2 eptifibatide) at the beginning of the intervention which is the standard practice at our institution.[5,6] If necessary, supplemental boluses of UFH were administered to achieve a target activated clotting time (ACT) of at least 200 sec. ACT was measured using the Hemochron (ITC Technidyne Corp, Edison, NJ, USA) device.

Coronary Intervention

Coronary interventional procedures were performed according to standard techniques, via a femoral approach. The choice of drug-eluting stent or bare metal stent implantation was at the discretion of the operator. Femoral vascular closure devices (Angio-Seal [St. Jude Medical, Minnetonka, Minn., USA] or Perclose [Perclose Inc., Redwood City, Calif., USA]) were used, unless contraindicated. Serial monitoring of cardiac biomarkers was performed every 8 h for 24 h after PCI and hemoglobin levels were done every 24 h until the patient was discharged. At the time of discharge it was recommended that all patients take aspirin indefinitely and clopidogrel for at least 9 to 12 months.

Neutrophil to Lymphocyte Ratio

It is the routine policy in our cardiac catheterization laboratory that immediately after making a decision to proceed with intervention after diagnostic cardiac catheterization, all routine blood work including complete blood picture, basic metabolic panel, and cardiac enzymes are sent. Those patients who had a differential WBC count done just prior to the coronary intervention were collected. Among those patients who did not have a differential WBC count done just prior to intervention, neutrophil and lymphocyte counts done in that particular hospital admission closest to the PCI were collected. Only those patients who had differential WBC counts done in the index hospitalization were included in the current study. WBC and the differential counts were measured using the automated system Cell-Dyn 4000 (Abbott, Santa Clara, Calif., USA). A N/L ratio of above 3.5 was shown to be a marker for inflammation in some studies.[7,8] Accordingly, we stratified our patients into 2 groups based on this value.

Follow-Up

We used all-cause mortality as our long-term outcome. The Social Security Death Index[9] was used to determine the time of death as of April 23, 2008.

Statistical Analysis

Continuous variables are presented as mean±SD. Categorical variables are presented as percentages. A chi-square test was used to compare the differences between categorical variables. The independent samples *t* test was used to compare continuous variables with normal distribution and the Mann-Whitney U test was used to compare continuous variables without a normal distribution. Event free survival rates during the follow-up period were estimated by the Kaplan-Meier method and tested by the log-rank statistic. Multivariate Cox proportional hazards regression modeling was used to estimate the independent effect of N/L ratio in the study population. Sequential models were fit with the initial model including no covariates (unadjusted); the final model included covariates selected by stepwise methods which had significant impact ($p<0.05$) on all-cause mortality. Covariates tested in a stepwise fashion in the multivariable Cox proportional hazards regression model include age, gender, body mass index, indication for the procedure (non-ST-segment elevation myocardial infarction, unstable angina, and stable angina), history of any medical problems (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic renal insufficiency, end-stage renal disease), smoking history, family history of coronary artery disease, medications (beta-blockers, ACE inhibitors, and statins), type of platelet glycoprotein IIb/IIIa inhibitor used, left ventricular ejection fraction, total white blood count, target coronary artery, number of diseased vessels, multi-vessel intervention, type of stent used, length and diameter of the stents used, percentage stenosis of the vessels, and successful PCI. P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed utilizing SPSS software version 15.0 (SPSS, Chicago, Ill., USA).

Results

Baseline Characteristics

The baseline characteristics are listed in Table 1 and procedural characteristics are presented in Table 2. Non-ST-segment elevation myocardial infarction (NSTEMI) was a more common indication for PCI in the higher neutrophil to lymphocyte group (26.7% in the higher N/L ratio compared to 13.1% of patients in the lower N/L ratio; $p = 0.024$). Abciximab was the most frequently used GPI in patients with higher N/L ratio (55.6% versus 30.3%, $p = 0.001$). Tirofiban was more frequently used in lower N/L ratio group compared to the higher N/L ratio group (26.3% versus 11.1%, $p = 0.026$). Drug-eluting stents were more frequently used in patients with lower N/L ratio group (52.6% compared to 35.6% in the higher neutrophil to lymphocyte count group, $p = 0.038$).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20503

Table 1. Baseline characteristics

	N/L<3.5	N/L≥3.5	p value
Age (mean±SD in years)	62.5±10.6	64.5±12.4	0.54
Females, n (%)	149 (45.6)	19 (42.2)	0.75
BMI (mean±SD, kg/m²)	30.1±6.4	29.7±6.8	0.44
Indication, n (%)			
NSTEMI	43 (13.1)	12 (26.7)	0.024
Unstable Angina	142 (43.4)	17 (37.8)	0.52
Stable Angina and Others	145 (44.3)	15 (33.3)	0.2
Medical History, n (%)			
Hypertension	293 (89.6)	41 (91.1)	1.0
Diabetes Mellitus	143 (43.7)	26 (57.8)	0.08
LV Dysfunction	80 (24.5)	13 (28.9)	0.58
Smoking	89 (27.2)	10 (22.2)	0.59
Family History	88 (26.9)	7 (15.6)	0.14
Previous CAD	183 (56)	21 (46.7)	0.26
CRI (Creatinine >1.5 mg/dl)	81 (24.8)	17 (37.8)	0.07
ESRD	21 (6.4)	6 (13.3)	0.12
GP IIb/IIIa inhibitor, n (%)			
Abciximab	99 (30.3)	25 (55.6)	0.001
Eptifibatide	142 (43.4)	15 (33.3)	0.26
Tirofiban	86 (26.3)	5 (11.1)	0.026
Medications, n (%)			
Beta-blocker	264 (80.7)	38 (84.4)	0.68
Statin	267 (81.7)	34 (75.6)	0.32
ACE inhibitor	227 (69.4)	28 (62.2)	0.39
Ejection Fraction (Mean±SD)	52.6±11.8	51.2±12.2	0.36
WBC (Mean±SD)	6.2±1.9	8.1±2.4	<0.001

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CRI = chronic renal insufficiency; ESRD = end-stage renal disease; GP = glycoprotein; LV = left ventricle; N/L = neutrophil to lymphocyte ratio; NSTEMI = non-ST-segment elevation myocardial infarction; SD = standard deviation; WBC = white blood cell count.

Table 2. Procedural characteristics

	N/L<3.5	N/L≥3.5	p value
Target Coronary Artery, n(%)			
Left Main	7 (2.1)	0 (0)	1.0
Left Anterior Descending	126 (38.5)	17 (37.8)	1.0
Left Circumflex	78 (23.9)	15 (33.3)	0.2
Right Coronary Artery	108 (33)	13 (28.9)	0.62
Others (ramus intermedius, LIMA and SVG)	12 (3.7)	3 (6.7)	0.41
Number of Vessels Involved, n(%)			
Single Vessel Disease	129 (39.4)	17 (37.8)	0.87
Double Vessel Disease	93 (28.4)	12 (26.7)	0.86
Triple Vessel Disease	105 (32.1)	16 (35.6)	0.73
Stents, n(%)			
Bare metal	151 (46.2)	28 (62.2)	0.056
Drug-eluting	172 (52.6)	16 (35.6)	0.038
Multi-vessel Intervention, n(%)	5 (1.6)	2 (4.5)	0.2
Mean Peak ACT±SD	279±68	272± 57	0.93
PCI Successful, n(%)	315 (99.7)	43 (97.7)	0.23
Mean Number of Stents±SD	1.2±0.6	1.3±0.7	0.57
Mean Length of the Stent±SD	16.6±6.2	16.0±5.3	0.59
Mean Diameter of the Stent±SD	3.2±0.5	3.2±0.4	0.21
% Stenosis of Target Lesion±SD	82±10	84±11	0.26

Abbreviations: ACT = activated clotting time; LIMA = left internal mammary artery; N/L = neutrophil to lymphocyte ratio; PCI = percutaneous coronary intervention; SD = standard deviation; SVG = saphenous venous graft.

All-cause Mortality

During the median (± SD) follow-up period of 3.6 – 1 years, there were a total of 48 deaths. The mortality rate was 10.4% in the group with lower N/L ratio and 31.1% in the group with higher N/L ratio (unadjusted p<0.001; Figure 1).

After adjustment for covariates with significant impact on mortality (Table 3) N/L ratio was a strong and independent predictor of long-term mortality with a hazard ratio of 2.1 (95% CI: 1.1–4; p = 0.02) at the end of the follow-up period.

We also analyzed N/L ratio as a categorical variable stratified into 3 groups with cut offs of N/L ratio at the 33rd percentile (N/L ratio = 1.57) and 66th percentile (N/L ratio = 2.39) when arranged in ascending order. The mortality in the lower tertile with N/L ratio between 0–1.57 was 9% compared to 8.1% in the middle tertile with N/L ratio between 1.58–2.39 and 22% in the upper tertile with N/L ratio over 2.39 (unadjusted p = 0.001). After adjustment for covariates with significant impact on mortality, the difference in mortality between the lower tertile and the

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20503

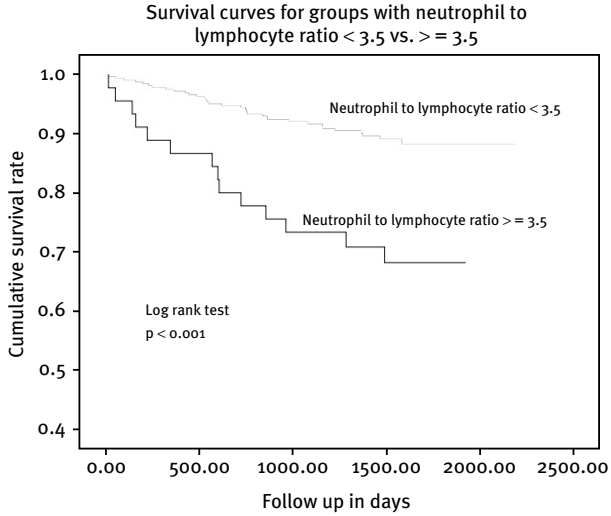

Figure 1. Kaplan-Meier survival curves according to neutrophil to lymphocyte ratio <3.5 or ≥3.5. At 3.6±1 y, the survival rate was 89.6% in the group with neutrophil to lymphocyte ratio <3.5 compared to 68.9% in the arm with neutrophil to lymphocyte ratio ≥ 3.5 (p<0.001 by log-rank test).

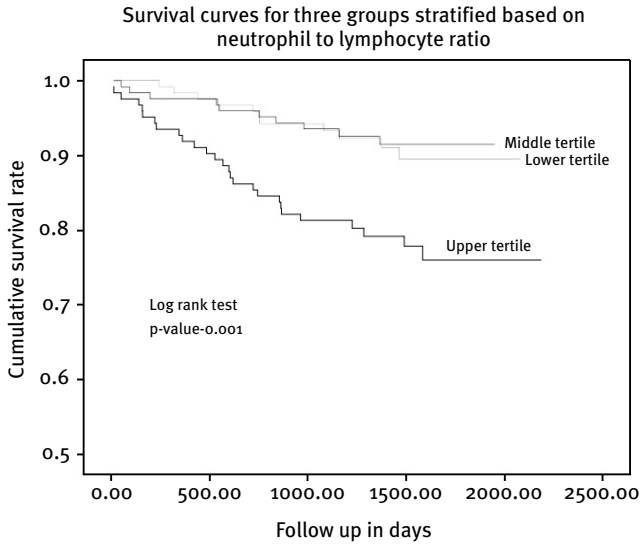

Figure 2. Kaplan-Meier survival curves according to neutrophil to lymphocyte ratio stratified into 3 groups with cut offs at 33rd percentile and 66th percentile of neutrophil to lymphocyte ratio when arranged in ascending order. At 3.6±1 y, the survival in the lower tertile was 91% compared to 91.9% in the middle tertile and 78% in the upper tertile with neutrophil to lymphocyte ratio over 2.39 (p = 0.001 by log-rank test).

upper tertile was still significant with a hazard ratio of 0.39 for the lower tertile compared to the upper tertile (95% CI: 0.19–0.81; p = 0.012; Figure 2).

Table 3. Multivariate predictors of all-cause mortality at the end of follow-up period (3.6±1 y)

Variable	Hazard Ratio	95% CI	p value
N/L Ratios≥3.5	2.114	1.11–4.02	0.023
Body Mass Index	0.924	0.88–0.97	0.004
CRI (Creatinine >1.5)	3.232	1.64–6.38	0.001
Diabetes Mellitus	2.601	1.37–4.95	0.004
End-Stage Renal Disease	7.342	3.25–16.6	<0.001
Multi-Vessel Intervention	6.758	1.2–22.9	0.002

Abbreviations: CRI = chronic renal insufficiency; N/L ratio = neutrophil to lymphocyte ratio.

Finally we also analyzed N/L ratio as a continuous variable and again found it to be a strong and independent predictor of long-term mortality with predictor of long-term mortality (p = 0.002).

Discussion

Our study shows that the N/L ratio is a strong and independent predictor of long-term mortality in African Americans undergoing PCI. Although there is evidence suggesting a relationship between the N/L ratio and mortality in patients undergoing PCI,[3] African Americans who tend to have lower neutrophil counts[4] and similar lymphocyte counts compared to their white counterparts have never been studied in this regard.

Previous studies have shown that PCI stimulates an acute inflammatory response at the site of intervention associated with increase in neutrophil, monocyte, and platelet adhesion molecule expression and activation of neutrophils.[10,11] White blood cell count has been shown to be a predictor of angiographic findings[12] and an independent predictor of long-term mortality after PCI.[13,14] Among the patients at risk for coronary artery disease, higher neutrophil counts and lower lymphocyte counts were associated with higher risk of death or MI. These previously reported associations are consistent with our findings that the N/L ratio appears to be a powerful predictor for long-term mortality after PCI.

Our study results are consistent with the study by Duffy et al.,[3] who showed that N/L ratio is a powerful predictor of long-term mortality after PCI. Our intention is to extend these results to the African American population, which has been shown to have lower neutrophil counts and similar lymphocyte counts compared to whites. Another justification for the current study is that active smokers have been shown to have higher leukocyte and neutrophil counts compared to those who never smoked.[4] However, African American smokers had a smaller increase in leukocyte and neutrophil counts compared to white smokers suggesting that the WBC response in certain conditions in

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20503

African Americans may be suboptimal compared to whites.[15] Despite the differences in WBC in these 2 ethnic groups, N/L ratio appears to be a strong predictor of long-term mortality in both groups.

Our study has a number of limitations. The major limitation of our study is that only 52% of the African Americans in our database had differential WBC counts measured prior to PCI as obtaining differential WBC is not a routine test prior to PCI. This could lead to selection bias. Even in the study by Duffy et al.[3] less than 25% of the study population had differential WBC counts available. However, in our study, the impact of neutrophil to lymphocyte was analyzed using 2 different stratifications and also as a continuous variable, which consistently showed that N/L ratio is an independent predictor of long-term mortality. Another major limitation of our study is small sample size. Common predictors of long-term mortality like age and left ventricular ejection fraction are not multivariate predictors of long-term mortality in our model probably due to the small sample size. This study is a retrospective analysis and has all the inherent limitations of a retrospective study. The baseline and procedural characteristics between the 2 groups were reasonably similar, but there were certain differences which had to be adjusted. In particular, the group with a higher N/L ratio appeared to have a higher risk patient population due to more patients with NSTEMI. Despite adjustment, there could be residual confounding variables that could lead to the observed differences in outcomes between the 2 groups. We excluded patients with STEMI. We included all-cause mortality as our endpoint and we excluded those patients without a valid social security number that might have introduced a selection bias. However, all-cause mortality is considered the most unbiased endpoint in long-term outcomes studies, especially if they are retrospective, as other chronic medical conditions may affect the attributed cause of death.[16,17]

Despite these limitations, we conclude that the N/L ratio is an independent predictor of long-term mortality in African American patients undergoing PCI. These observations would best be confirmed in large randomized controlled studies.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20503