Association between Neutrophil-To-Lymphocyte Ratio and Incidence of Contrast Induced Nephropathy among Adults Undergoing Percutaneous Coronary Intervention

---

Marion B. Sarigumba, M.D.[1], Filoteo C. Ferrer, M.D.[2]

[1]Resident, Department of Medicine

[2]Consultant, Department of Medicine

Makati Medical Center

2 Amorsolo St. Legaspi Village, Makati City 1229

Tel. No. (02) 420 7460

Email address: marionsarigumba@gmail.com

ABSTRACT

INTRODUCTION: Though the role of inflammation is reputedly associated with contrast induced nephropathy (CIN), especially in the setting of Acute Coronary Syndrome (ACS), current risk scoring systems do not address inflammatory factors. Neutrophil lymphocyte ratio (NLR), a proportion of two inflammatory markers, is reflective of the balance between innate and adaptive immune responses, and therefore has a strong predictive value.

METHODS: A cross-sectional analytical study done among adult Filipinos diagnosed with ACS who underwent Percutaneous Coronary Intervention (PCI) from January to December 2018 at Makati Medical Center. Exposure of interest includes baseline NLR count and pre-procedural serum creatinine. Outcome was the incidence of CIN based on serum creatinine 24-48 hours post-procedure.

RESULTS AND ANALYSIS: A total of 166 ACS patients were analyzed, of which 11 (6.62%) has CIN. Patients with pre-procedural NLR $\geq$ 4.71 were approximately five times as likely to develop CIN (aOR 1.51 to 17.55, p = 0.009), with sensitivity 63.64%, specificity 80.65%, accuracy 79.52%, Youden's index 44.29%. On multivariate analysis, NLR and STEMI were associated with increased odds for CIN. STEMI patients had approximately four times the odds of developing CIN (aOR 3.893, 95% CI 1.07 to 14.13, p = 0.039).

CONCLUSION: NLR $\geq$ 4.71 in Filipinos with ACS who underwent PCI is associated with increased risk to develop CIN.

KEYWORDS: Neutrophil-to-lymphocyte ratio, contrast induced nephropathy

I. INTRODUCTION

The burden of ischemic heart disease is significant on a global scale. It was the top leading cause of death in the Philippines in 2016, accounting for 74, 134 or 12.7 percent of the total.[1] Ischemic heart disease (IHD) typically occurs when there is imbalance between myocardial oxygen supply and demand. Patients with IHD fall into two large groups, those with chronic coronary artery disease and patients with acute coronary syndrome. The latter include patients with ST segment elevation myocardial infarction (STEMI) and acute coronary syndrome non-ST elevation (ACS-NSTE), which encompasses unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI). [2]

Percutaneous coronary intervention (PCI), in the form of angioplasty or stenting, is effective in restoring perfusion in STEMI when done on an emergency basis during the first hours of MI. Primary PCI refers to the procedure when there is no preceding fibrinolysis. It is generally preferred in certain conditions, including the following: 1 when diagnosis is in doubt, 2 presence of cardiogenic shock, 3 increased bleeding risk, 4 symptoms present for at least 2-3 hours. [2]

Contrast-induced nephropathy (CIN) is a generally reversible form of acute kidney injury that may occur after administration of contrast media for either diagnostic or therapeutic purposes including PCI. It usually goes unrecognized, as it is asymptomatic. With the wide application of PCI in patients diagnosed with coronary artery disease, CIN has become one of the most serious complications, particularly in those patients with acute coronary syndrome, and correlates with increased adverse clinical outcomes.[3]

The pathogenesis of CIN is not completely understood and multiple mechanisms may be involved. There is no effective treatment for CIN, which emphasizes the need for clinical prevention efforts. Several studies demonstrated a close relationship between the systemic inflammatory marker levels being at high risk for acute renal insufficiency after contrast media exposure in ACS and stable coronary artery disease. Though inflammation is reported to play an important role in the development of CIN, especially in the setting of ACS, the popularized risk score models such as Mehran's and Bartholomew's, do not address inflammatory factors.[3] In addition to increased inflammatory response, previous studies have shown that decrease

renal blood flow, increased oxidative stress, renal parenchymal hypoxia and direct tubular toxic effect of contrast media may also be responsible for the development of CIN.[4]

The neutrophil-to-lymphocyte ratio (NLR) is a useful and reliable inflammatory prognostic marker for predicting adverse outcomes in various cardiovascular diseases. White blood cells, namely monocytes, lymphocytes, and neutrophils, are known to play a critical role in the inflammatory response. NLR is calculated as the proportion of two inflammatory markers, neutrophil and lymphocytes. It is known to be reflective of the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses, and therefore has a strong predictive value.[15]

There is wide use of hematologic markers in clinical practice. However, despite being inexpensive and simple, its utility can be exigent due to its lack of standardization and evidence. In this era of prevention, it is valuable to identify the problem in time than seek a remedy after the damage is done. Establishing the optimal cut-off level of specific biomarkers at which disease progression can be predicted is essential. Given the role of inflammation in damage and pathogenesis of CIN, this study aims to evaluate the association of NLR with development of CIN in NSTE-ACS and STEMI patients who underwent PCI.

II. METHODS

This cross-sectional analytical study was approved by the Institutional Review Board of Makati Medical Center (protocol number: 2019-022; date of approval: May 27, 2019).

Medical charts of all adults (40 years or older) diagnosed with acute coronary syndrome who underwent percutaneous coronary intervention admitted in Makati Medical Center from January 1 to December 31, 2018 were reviewed. Retrospective data review was done on an electronic medical record system. A total of 507 patients was reviewed, of which 341 patients (67.26%) were excluded. Major reasons for exclusion included the following: lack of both pre-operative and post-operative laboratory tests, including CBC and serum creatinine (238 of 341, 69.79%) and the lack of pre-operative laboratory tests alone (63 of 341, 18.48%).

Baseline characteristics of the patients (age, sex, BMI, co-morbidities) were accounted for together with results of blood tests (serum creatinine, baseline CBC). Hematologic measurements using XN-1000 hematology analyzer were carried out by the in-hospital

laboratory department who conducts internal quality control every 12 hours and external quality control monthly. NLR was calculated by dividing neutrophil count by lymphocyte count. Serum creatinine was measured on admission prior to the PCI and 24-48 hours after. CIN is considered to be positive when there is an increase in serum creatinine of 0.3 mg/dl or greater within 48 hours of contrast use, as defined by the Kidney Disease Global Outcome Guidelines (2012).

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for continuous variable. Mann-Whitney U test and Fisher's exact were used to determine the difference of median and frequency between CIN+ and CIN-, respectively. Receiver operating characteristic (ROC) curves was plotted to determine the optimal cut-off value for NLR in predicting CIN. Youden's J index was defined for all points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the best cut-off point. Firth logistic regression or the panelized likelihood estimation method was used to determine the factors associated with contrast induced nephropathy. Firth regression provides bias reduction for rare events. All valid data was included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level significance. STATA 15.0 was used for data analysis.

III. RESULTS

We analyzed a total of 166 ACS patients, of which 11 (6.62%) has contrast induced nephropathy. Overall, they had a median age of 57.5 years, and predominantly male (82%) and NSTEMI (69%). Between the two groups, the CIN+ patient had a larger proportion of STEMI compared to CIN- (63.37% vs 29%, p = 0.037).

Table 1. Baseline characteristics of patients with acute coronary syndrome (n = 166)

	Total (n = 166)	CIN+ (n = 11)	CIN- (n = 155)	p-value
	Frequency (%); Mean ± SD; Median (Range)			
Age, years	57.5 (40-74)	59 (45-67)	57 (40-74)	0.619*
Sex				1.000†
Male	136 (81.93)	9 (81.82)	127 (81.94)	
Female	30 (18.07)	2 (18.18)	28 (18.06)	
Height (cm)	167 (146-183)	167 (154-174)	167 (146-183)	0.943*
Weight (kg)	74.5 (40.8-140)	72 (45-111)	75 (40.8-140)	0.673*
BMI (kg/m^2)	26.86 (17.9-52.6)	26.64 (18.97-37.09)	27 (17.9-52.6)	0.719*
SBP	130 (80-250)	130 (100-147)	130 (80-250)	0.787*
DBP	80 (43-167)	80 (60-97)	80 (43-167)	0.788*
Heart rate	79.5 (45-167)	87 (57-140)	79 (45-167)	0.568*
Neutrophil	63.5 (38-93)	80 (55-87)	63 (38-93)	**0.008***
Lymphocyte	24 (4-51)	14 (7-33)	25 (4-51)	**0.013***
NLR	2.53 (0.76-23.25)	5.5 (1.67-11.71)	2.48 (0.76-23.25)	**0.008***
ACS type				**0.037†**
NSTEMI	114 (68.67)	4 (36.36)	110 (70.97)	
STEMI	52 (31.33)	7 (63.64)	45 (29.03)	
Comorbidities				
DM	78 (46.99)	7 (63.64)	71 (45.81)	0.351†
Hypertension	112 (67.47)	5 (45.45)	107 (69.03)	0.179†
Dyslipidemia	34 (20.48)	3 (27.27)	31 (20)	0.698†
Hypotension	3 (1.81)	0	3 (1.94)	1.000†
Smoking				0.492†
Never	86 (51.81)	8 (72.73)	78 (50.32)	
Previous	33 (19.88)	1 (9.09)	32 (20.65)	
Current	47 (28.31)	2 (18.18)	45 (29.03)	
Previous history of CAD	24 (14.46)	1 (9.09)	23 (14.84)	1.000†
Family history of CAD	37 (22.29)	2 (18.18)	35 (22.58)	1.000†

Statistical Tests Used: * - Mann Whitney U test; † - Fisher's Exact test

The CIN+ group had significantly higher neutrophil count (80 vs 63, p = 0.008) and significantly lower lymphocyte count (14 vs 25, p = 0.013).

Table 2. Biochemical and hematologic parameters of patients with acute coronary syndrome (n = 166)

	Total (n = 166)	CIN+ (n = 11)	CIN- (n = 155)	p-value
	Frequency (%); Mean ± SD; Median (Range)			
Neutrophil	63.5 (38-93)	80 (55-87)	63 (38-93)	**0.008**
Lymphocyte	24 (4-51)	14 (7-33)	25 (4-51)	**0.013**
NLR	2.53 (0.76-23.25)	5.5 (1.67-11.71)	2.48 (0.76-23.25)	**0.008**
WBC	9.2 (4-19.6)	11.2 (4-17.71)	9.09 (4.03-19.6)	0.057
Hemoglobin	14.2 (8.4-43.7)	14.1 (11.5-16.7)	14.2 (8.4-43.7)	0.920
Creatinine				
Baseline	1.09 (0.26-2.84)	1.11 (0.55-1.42)	1.09 (0.26-2.84)	0.902

Post [n=165]	1.04 (0.39-3.5)	1.7 (1-3.5)	1.01 (0.39-2.71)	**<0.001**
Platelet	269.5 (111-438)	282 (161-377)	268 (111-438)	0.577

Statistical Test Used: Mann Whitney U test

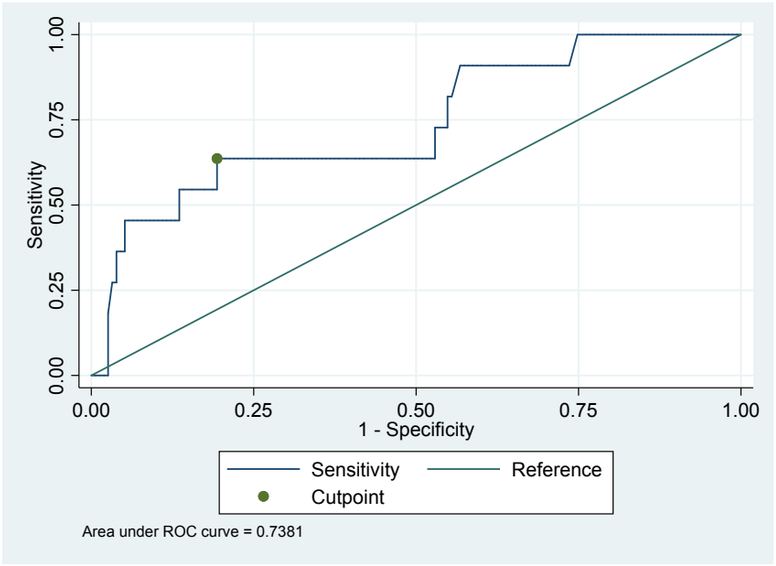


Figure 1. Receiver–operating characteristic (ROC) curve analysis plot to determine the cutoff value of neutrophil-to-lymphocyte ratio in the prediction of contrast-induced nephropathy. AUC = 0.7381. Suggested optimal cutoff NLR is ≥ 4.71, with sensitivity 63.64%, specificity 80.65%, accuracy 79.52%, Youden's index 44.29%

Since CIN is a rare event, occurring only in 11/166 patients, we performed Firth logistic regression to determine the association between contrast induced nephropathy and NLR among ACS patients. On multivariate analysis, we noted NLR to be associated with increased odds for CIN, after adjusting for age, sex, BMI, baseline creatinine, ACS type, and comorbidities (Table 3).

Patients who had an NLR ≥ 4.71 were approximately five times as likely to develop CIN (aOR 4.62. 95%CI 1.39 to 15.32, p = 0.012). The model on Table 3 explains for 31.4% of the variation in CIN outcome, but was not statistically significant at p = 0.1934.

Table 3. Factors associated with Contrast Induced Nephropathy in patients with Acute Coronary Syndrome (n = 166)

	Crude Odds Ratio (95% CI)	**p-value**	**Adjusted Odds Ratio (95% CI)**	**p-value**
Age, years	0.980 (0.91 – 1.06)	0.600	0.992 (0.91 – 1.08)	0.852
Sex				
Male	Reference	-	Reference	-
Female	1.177 (0.28 – 5.02)	0.826	1.888 (0.38 – 9.27)	0.434
BMI (kg/m^2)	0.990 (0.87 – 1.13)	0.882	0.993 (0.85 – 1.16)	0.932
Baseline creatinine	0.743 (0.11 – 4.86)	0.757	0.936 (0.14 – 6.18)	0.945
ACS type				
NSTEMI	Reference	-	Reference	-
STEMI	**4.048 (1.20 – 13.69)**	**0.025**	3.076 (0.82 – 11.51)	0.095
Comorbidities				
DM	1.970 (0.59 – 6.61)	0.272	2.574 (0.68 – 9.76)	0.164
Hypertension	0.382 (0.12 – 1.25)	0.111	0.538 (0.15 – 1.93)	0.341
Dyslipidemia	1.627 (0.44 – 6.00)	0.464	1.880 (0.46 – 7.75)	0.382
Hypotension	1.894 (0.09 – 38.94)	0.679	1.916 (0.09 – 42.35)	0.681

NLR				
<4.71	Reference	-	Reference	-
≥4.71	**6.858 (2.00 – 23.55)**	**0.002**	**4.616 (1.39 – 15.32)**	**0.012**

Adjusted R^2(Nagelkerke R^2): 31.4%; p-value: 0.1934

IV. DISCUSSION

This present study demonstrates a significant association between NLR and risk for CIN among adults who underwent PCI. Results showed that elevated admission NLR is associated with increased risk for CIN. Optimal cut-off NLR in this study done among Filipino population is ≥ 4.71 with a sensitivity of 63.64%, specificity of 80.65% and accuracy of 79.52%. Patients with NLR above of this value were approximately five times as likely to develop CIN, more commonly in ACS-STEMI population.

In a similar study done by Kaya et al in 2013 that involved 691 STEMI patients, both NLR and C-reactive protein levels were significantly higher in the CIN group. It showed that NLR, which is a detectable marker of systemic inflammation, has a significant and independent relationship with the development of CIN. NLR may therefore be used as a simple and reliable indicator of CIN in patients with STEMI who underwent coronary intervention.[6]

Previous retrospective and prospective studies reviewed have suggested high-risk cut-off levels of pre-treatment NLR from Kaplan-Meier curves and multivariate Cox-regression analysis. However, these studies discounted some important attributes, including disease category, age and race of patients, which are paramount in applying the findings to clinical situations.[7] There have been no reported standardized levels for this biomarker to demonstrate significance of a value higher than that of an average healthy patient.[8]

To the best of our knowledge, this is the first study conducted in a Filipino population to determine the association between NLR and incidence of CIN among patients post PCI. In 2015, a similar study was done in Ankara, Turkey that included 478 patients with NSTE-ACS who underwent PCI. Results showed that increased NLR (≥ 3.46) is independently associated with risk of CIN in NSTE-ACS patients treated by PCI. Among Asian population, a retrospective data review was done in South Korea in 2018 that provided preliminary reference data on NLR according to sex and age of more than 10,000 patients from a single racial group. The results of the study suggested that different cut-off values should be applied to various patient populations. It stated that NLR in the Asian population was generally lower than other races

with mean NLR across all ages in men and women of 1.63 (0.76) and 1.66 (0.82), respectively. A study of the average value and racial difference in the United States reported that the NLR was higher than 2 in all races except non-Hispanic black patients. [7]

Neves et al in 2016 proved in a study with a total of 11, 812 patients included that STEMI patients seem to be at greatest risk for developing CIN. This expected finding stems from their representation of ACS patients with greatest hemodynamic impact and/or lowest hemodynamic and renal functional reserve.[9]

Renal vascular endothelium and tubular epithelium go through changes, both structural and functional, under unfavorable conditions such as ischemia, sepsis and nephrotoxic effects. On top of this, the inflammatory cells, such as macrophages, natural killer cells, lymphocytes, and particularly neutrophils, pervades damaged tissues which further aggravates renal destruction.[10] Overactivation of neutrophils furthermore increases the release of cytokines, reactive oxygen species, proteases, elastases, and many enzymes, which enhances vascular permeability and disrupts endothelial functions.[11] Ultimately, this endothelial damage leads to reduced vasodilator response, elevated vasoconstrictor arachidonic acid metabolites, increased adhesion and aggregation of platelets causing physical obstruction of capillaries, which in turn may lead to reduced blood flow, exaggerated ischemic damage, and destruction in the normal tissue.[12]

The incidence of CIN varies widely across references. While in prospective studies CIN incidence is around 3.3%, in the particular subgroup of patients who had myocardial infarction requiring primary angioplasty, CIN incidence rises to 19%. [13] In accordance with previously published studies, timely risk allocation is important since patients with CIN had significantly higher in-hospital mortality, incurred increased costs and prolonged hospital stay. Its treatment is also rather limited. Once it has been established, only supportive care is currently proposed until resolution of renal injury and rarely, hemodialysis may be necessary either transiently or for long term. For these reasons, novel biomarkers are valuable tools to aid us in predicting its occurrence to potentially decrease its incidence and change the clinical course. With this, physicians could strike a balance between the risk and benefits of coronary angiography and/or PCI, select the optimal timing to carry out the procedure and ultimately,

optimize CIN prophylactic therapy prior and after catheterization. More aggressive preventive strategies are therefore warranted in patients at high risk. To date, there are numerous ways employed to prevent CIN but the cornerstone is maintenance of euvolemia as this prevents activation of both sympathetic and angiotensin-aldosterone systems.

It is also noteworthy that in this study, majority of the patients excluded had no baseline CBC and serum creatinine and routine post-operative laboratory surveillance. It should be highlighted that CIN has long been widely recognized and studied since the initial reports in the 1950s. With this established risk, physicians should be more cautious and act in a way that would not do more harm.

The study is not without limitations. First, the retrospective single-center study design with a relatively small sample size is inherently prone to bias. As with any retrospective review, there are limitations in data available. The amount of fluids or pre-operative medications given to patients and the total time of procedure, including amount of contrast used were not controlled. To improve this, a prospective randomized control trial with a larger population group to look into the association of NLR and CIN among patients with ACS undergoing PCI should be conducted. Re-assessment of renal function in our study was performed one to two days following PCI. Any further increase in serum creatinine after two days was not accounted for which may result in slight underestimation of CIN. Only NLR was measured in the study and no comparison with other inflammatory biomarkers because they were not routinely measured in our study population. Determination of left ventricular ejection fraction was also not possible, as a pre-procedural 2D-echocardiogram was not routinely done in all of the subjects. Lastly, possible disparities in the methods and timing of blood collection could alter the composition of the blood cells.

V. CONCLUSION

In conclusion, neutrophil-to-lymphocyte ratio $\geq$ 4.71 in adult Filipinos diagnosed with ACS who will undergo PCI, most notably ST elevation myocardial infarction, is associated with increased risk to develop CIN.

REFERENCES

1. Bersales, L. (Feb 2018). *Deaths in the Philippines, 2016.* Retrieved from https://psa.gov.ph/content/deaths-philippines-2016
2. Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L. 1., Jameson, J. L., & Loscalzo, J. (2015). *Harrison's principles of internal medicine* (19th edition.). New York: McGraw Hill Education.
3. Yuan Y, Qiu H, Hu X, Luo T, Gao X & Zhao X, et al. (2017) Predictive value of inflammatory factors on contrast-induced acute kidney injury in patients who underwent an emergency percutaneous coronary intervention. *Clin Cardiol.* 40 (9), 719-725
4. Kurtul A, et al. (2016) Association of Neutrophil-to-lymphocyte Ratio with Contrast-induced Nephropathy in Patients with Non-ST-elevation Acute Coronary Syndrome Treated with Percutaneous Coronary Intervention. *Heart, Lung and Circulation*. 25 (7), 683-690
5. Nunez J, Nunez E, Bodi V, et al. (2008) Usefulness of the neutrophil to lym- phocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol* 101(6), 747-752.
6. Kaya A et al. (2013) Neutrophil-to-lymphocyte ratio predicts contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention. *Angiology* 65(1), 51-56.
7. Lee JS, Kim NY, Na SH, Youn YH, Shin CS. (2018) Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine (Baltimore)*. 97(26): e11138. Doi: 10.1097/MD.0000000000011138
8. Azab B, Camacho-Rivera M, Taioli E (2014) Average Values and Racial Differences of Neutrophil Lymphocyte Ratio among a Nationally Representative Sample of United States subjects. *PLoS One.* 9 (11):e112361 doi: 10.1371/journal.pone.0112361
9. Neves D, Belo A et al. (2016). Acute kidney injury in acute coronary syndromes – An important multifactorial consequence. *Portuguese Society of Cardiology*. 24, 415-421
10. Akcay A, Nguyen Q, Edelstein CL. (2009) Mediators of inflammation in acute kidney injury. *Mediators Inflamm*. 2009:137072. doi:10.1155/2009/137072
11. Kinsey GR, Li L, Okusa (2008) Inflammation in acute kidney injury. *Nephron Exp Nephrol.* 109(4):e102-e107
12. Forman MB, Virmani R, Puett DW. (1990) Mechanisms and therapy of myocardial reperfusion injury. *Circulation*. 81(3): IV69-IV78.
13. Gorriz Teruel JK, Beltran Catalan S. (2011) Assessment of renal function, iatrogenic hyperkalemia and acute renal dysfunction in cardiology. Contrast-induced nephropathy. *Rev Esp Cardiol* 64 (12): 1182-1192

14. Lang EK, Foreman K, Schlegel JU, Leslie C, List A, McCormick P. (1981) Incidence of contrast medium induced acute tubular necrosis. *Radiology*. 138(1), 203-206
15. Manske CL, Sprafka JM, Strony JT, Wang Y. (1990) Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *AM J Med.* 89(5), 615-620
16. Hajian-Tilaki K. (2014) Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform.* 48, 193 – 204. Accessed from https://www.ncbi.nlm.nih.gov/pubmed/24582925.
17. Lazaro VL. (2014) PHA Clinical Practice Guidelines for the Diagnosis and Management of Patients with Coronary Heart Disease. *ASEAN Heart Journal : Official Journal of the ASEAN Federation of Cardiology*. 24(3). doi:10.7603/s40602-016-0003-6.