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The Effect of Preoperative Neutrophil-Lymphocyte Ratio on Quality of Life after Coronary Artery Bypass Graft (CABG) Surgery

Fatmawati Kamal, Roihan Awg Isa, Zalizah Khalid, Ummi Mohlisi Mohd Asmawi

Department of Pathology, Faculty of Medicine,
Universiti Teknologi MARA, Malaysia

fatmawati.kamal@gmail.com, aiwraihan@hotmail.com, zalizah@salam.uitm.edu.my, umieasmawi@salam.uitm.edu.my
Tel: 0136265250

Abstract

Neutrophil-lymphocyte ratio (NLR) is an inexpensive and easily accessible inflammatory biomarker. Studies have shown the ability of NLR to predict poor outcome in many diseases. This study aimed to determine the relationship between NLR and cardiovascular risk factors, and duration of ICU and hospital stay in post CABG patients. 137 patients who underwent CABG between 2013 and 2017 with available preoperative neutrophil and lymphocyte counts were included in the study. NLR was found to be increased in patients who had prolonged intensive care unit (ICU) stay and hospital/ ward stay. Thus NLR can potentially be used to predict worse outcome.

Keywords: Neutrophil-lymphocyte ratio; coronary artery bypass graft (CABG); mortality; length of stay (maximum 4 keywords)

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1.0 Introduction

Inflammation is known to play a role in atherogenesis and coronary artery diseases. There are also genetic and environmental factors involved in the process. Coronary artery disease (CAD) has become a major cause of death worldwide. Many studies were done to find a predictive tool to better prognosticate patients with CAD. Neutrophil-lymphocyte ratio was found to be a potential tool because it is inexpensive and easy accessibility. Moreover, many studies demonstrated increased NLR to independently predict a worse outcome in various medical conditions, unlimited to cardiovascular diseases. NLR reflects the balance between neutrophils and lymphocytes i.e. a high circulating neutrophils together lymphopenia, are suggesting ongoing inflammation. Its association with risk factors such as Type 2 diabetes mellitus has also been reported in the literature. Despite the many studies done on NLR, no cut-off value has been specified for NLR. Because of the lack of the reference value, different studies will have different cut-off values. This study aims to determine whether the same potential applies to our patients after coronary bypass grafting. We also assessed the relationship between NLR and cardiovascular risk factors such as smoking, T2DM and hypertension.

2.0 Literature Review

Coronary artery disease (CAD) is a major cause of mortality and morbidity worldwide. According to the data from the World Health Organization (WHO), CAD was a cause of death in 98.9 per 100 000 population in Malaysia in 2012. The Global Burden of Disease reported in 2010 that CAD is the single leading cause of disease burden indicated by disability-adjusted life years (DALYs, calculated as the sum of years of life lost and years lived with disability) (Sergi Sayols-Baixeras, 2014). Clinical CAD presents as angina, myocardial

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infarction, sudden death and chronic heart failure (Henderson, 1996). It is caused by atherosclerosis and longstanding subclinical atheroma in medium and large-sized muscular arteries (F Brian Boudi, 2016).

Treatment of CAD includes managing the modifiable risk factors such as body weight, dietary intake and physical activity, together with the use of pharmacological therapies. Medications to control blood pressure, T2DM and cholesterol levels are included in the treatment regime. Invasive treatment like percutaneous transluminal coronary angioplasty (PCI) and coronary artery bypass grafting (CABG) are revascularization procedures available to treat CAD. CABG is said to be the most frequent surgical treatment performed with low periprocedural mortality (Abdullah Ozer, 2018). The SYNTAX study compared the long-term outcome between PCI and CABG and found that long-term mortality was similar between the two procedures in most patient subgroups with multivessel CAD (F Brian Boudi, 2016). In another study, PCI provided a more rapid recovery at one month compared to CABG. However, after six months, CABG provided greater angina relief and quality of life compared to PCI (Kulik, 2017). Most studies used the 36 short form health survey (SF-36) to assess the health-related quality of life, and reported good to excellent quality of life even after five years of CABG (Irene Lie, 2010; John S Rumsfeld, 2004; Josip Vincelj; Saccomann, 2013).

The idea that inflammation had an important role in the development of CAD came in the late 1990's. This idea was prompted by the increasing prevalence of CAD despite aggressive pharmacological treatment, especially in the developing countries (Massimo Fioranelli, 2018). Atherogenesis starts with endothelial injury leading to activation of the immune response and inflammation. The inflammatory cells involved are monocyte-derived macrophages and specific sub-types of lymphocytes. These cells can be seen in fatty streaks, which are the earliest form of atherosclerotic lesions (Alexander, 1994; Ross, 1999).

Neutrophil to lymphocytes ratio (NLR) has been a subject of many researches looking for a predictive tool to better prognosticate patients, and it is not only limited to cardiovascular diseases. Examples include research in cancer prognostication, identifying high risk vascular surgical patients, non-alcoholic fatty liver disease, Alzheimer's disease and appendicitis (Alexander J. Fowler, 2013). The first group to report the correlation between NLR and severity of CAD was Arbel et al. (Yaron Arbel, 2012). The greatest risk prediction was noted when NLR was more than 4.71 (Benjamin D. Horne, 2005). Neutrophils are involved in acute inflammation, as opposed to lymphocytes, which are involved in chronic inflammation. Lymphocytes are also seen as the regulatory and 'protective' component (Bhutta et al., 2011). Thus, the ratio of neutrophils to lymphocytes reflects the balance in the inflammatory process. It is calculated as a ratio of an absolute number of neutrophils to an absolute number of lymphocytes.

NLR is inexpensive and easily accessible. So far, results showed that it is an independent prognostic factor in many diseases (Balta S, 2016). In cardiovascular disease, a high NLR has been linked with increased risk of ventricular arrhythmias during PCI and long-term mortality in patients undergoing PCI irrespective of indications of PCI. It is also reported to correlate with poor outcome from CABG and post-CABG atrial fibrillation (Bhat T, 2013).

The aim of our study was to determine whether high NLR consistently correlates with poor outcome in patients after CABG. We also aimed to determine whether increased NLR is associated with common risk factors such as body mass index, smoking, Type II diabetes mellitus and hypertension.

3.0 Methodology

This is a descriptive, cross-sectional study, carried out at the Faculty of Medicine Universiti Teknologi MARA, Sg Buloh Campus. This study was approved by UiTM Research Ethics Committee, University Teknologi Mara (UiTM), Shah Alam on 27th March 2017. Review of patient's demographic data and risk factors were carried out anonymously and obtained for all patients, underwent CABG between June 2013 and December 2017. Results of complete blood count (CBC) were generated using automated haematology analyser Advia 2120i (Siemens Healthcare Diagnostics).

3.1 Inclusion Criteria

All patients aged between 20 to 80 years old who underwent primary isolated elective CABG between June 2013 to December 2017, with pre-operative neutrophil and lymphocyte counts and complete medical records were included in this study.

3.2 Exclusion Criteria

Exclusion criteria include emergency CABG, CABG within one week of acute myocardial infarction, active or chronic inflammatory disease, patients on steroid therapy, and intra-operative mortality.

3.3 Neutrophil-Lymphocyte Ratio (NLR)

Neutrophil-lymphocyte ratio were calculated from differential white count results in a laboratory database. It is calculated as the ratio of an absolute number of neutrophils to an absolute number of lymphocytes. The NLR were obtained within a week prior to CABG. NLR $\geq$ 2.5 is considered increased. All complete blood count (CBC) tests were performed using Siemens Advia 2120i haematology analyser.

3.4 Measurement of Outcomes

The unfavourable outcomes include mortality after CABG, prolonged ICU stay (more than 3 days), and prolonged hospital/ ward stays (more than 7days).

3.5 Risk factors analysis

The risk factors included in the analysis were body mass index (BMI), smoking status (smoker vs non-smoker) and other cardiovascular risk factors such as Type II diabetes mellitus (T2DM) and hypertension.

3.6 Statistical analysis

The data were recorded and analysed using the statistical package for social science (SPSS) version 25 software. Descriptive analysis including mean and standard deviation were used to describe demographic and clinical characteristics of patients who underwent CABG. Statistical analysis with simple t-test and regression analysis was performed to determine the association between the pre-operative NLR to the outcomes and risk factors.

4.0 Results

A total of 260 CABG were carried out between June 2013 and December 2017. Of 260, only 137 patients fulfilled the inclusion and exclusion criteria. Male constituted the majority of the patients, even when separated according to race. The majority of the patients were Malays, followed by Chinese and Indian. Most of the patients were in the 51 to 60 years old age group, followed by the 61 to 70 years old age group (Table 1). The mean age is 59 years old. The youngest patient who underwent CABG was 42 years old and the oldest was 74 years old. The mean age for male and female were 58.6 years old and 59.6 years old, respectively.

Table 1: Demographic data.

		Male	Female
	Mean		
Age (years)	59	58.6	59.5
Age group		n	n
41-50 (n=13)		13	0
51-60 (n=68)		52	16
61-70 (n=49)		37	12
71-80 (n=7)		7	0
Total		109	28
Race			
Malay (n=81)		65	16
Chinese (n=30)		25	5
Indian (n=26)		19	7

Table 2 illustrated the percentages of patients according to BMI. The mean BMI was 26.6 kg/m2 (CI:95%; 19.20kg/m^2-37kg/m^2). 55.5% of patients were overweight when they were admitted for CABG. BMI classification will follow WHO classification for BMI (Table 3). BMI is calculated as weight (kg) divided by height^2 (m)^2.

Table 2: Number of patients according to WHO BMI classification

BMI class	Number of patients (%)
18.5-24.9	29.9
25.0-29.9	55.5
≥30.0	14.6

Table 3: WHO Classification of Weight Status

WHO CLASSIFICATION OF WEIGHT STATUS	
WEIGHT STATUS	**BODY MASS INDEX (BMI), kg/m^2**
Underweight	<18.5
Normal range	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	≥ 30
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	≥ 40

Source: 1998 WHO report "Report of a WHO consultation on obesity. Obesity: preventing and managing the global epidemic".

Risk factors for CAD that were analysed in this study are smoking, Type II diabetes mellitus (T2DM) and hypertension. Review of data from patient's file showed that 46% were smokers, 70.8% had Type II diabetes mellitus and 88.3% had hypertension (Table 4). When matched for BMI ≥25-29.9 kg/m^2, 40.6% (n=39) of patients had both Type II diabetes mellitus and hypertension.

Table 4: Characteristics of patients according to smoking, diabetes mellitus and hypertension.

Characteristics	Mean (SD)	N (%)
Smoker		
Yes		63(46.0)
No		74(54.0)
Diabetes		
Yes		97(70.8)
No		40(29.2)
Hypertension		
Yes		121(88.3)
No		16(11.7)

4.1 Neutrophil lymphocyte ratio (NLR)

The mean NLR is 2.5 (± 2.8, CI: 95%; 0.81 – 11.44) and median NLR is 2.13. NLR ≥2.5 is considered increased in this study. 48 (35%) of 137 patients have NLR of 2.5 or more. In T2DM, the mean NLR was 2.67 compared to non-diabetic group, where the mean INR was 2.1 (p<0.05) (Table 5).

Table 5: Mean NLR according to T2DM

	T2DM		
	Yes (n= 97)	No (n=40)	p value
NLR (mean)	2.67	2.1	< 0.05

The association between increased NLR and smoking status and hypertension were not significant (p>0.05). The mean NLR in smokers was 2.6 and 2.4 in non-smokers. The number of smokers could be underestimated as it was based patient's response during history taking. Some patients might not be totally honest about their smoking status for various reasons. The mean NLR in hypertensive patients was 2.5 and 2.4 in non-hypertensive patients. In those who smoke, 39% had NLR ≥2.5. There was also no significant difference in NLR between patients who were overweight (BMI≥25kg/m^2) and those with normal BMI(Table 6). Figure 1 illustrated the distribution of NLR according to BMI. The mean NLR in patients with normal BMI was 2.26kg/m^2, compared to 2.6 in overweight patients.

Table 6: Mean NLR according to BMI

	BMI (kg/m^2)		
	<25 (n= 41)	≥25 (n=96)	p value
NLR (mean)	2.26	2.6	> 0.05

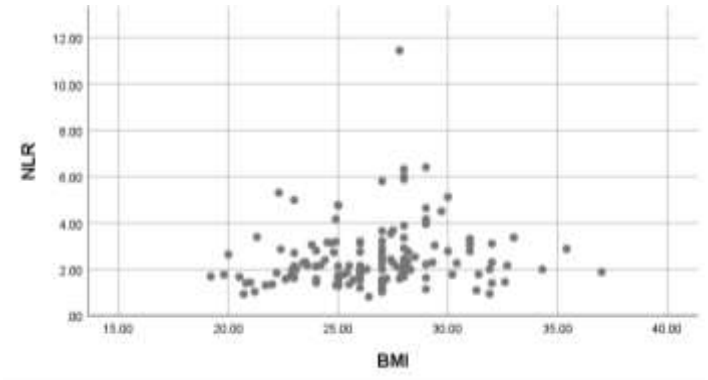

Figure 1: Simple scatter of NLR by BMI

4.2 Post-operative mortality

A total of 8 (5.8%) patients died within a week after CABG and 5 of them had NLR 2.5 or more. This is not clinically significant when all cases were compared.

4.3. Prolonged ICU stay (>3 days)

Ninety-six patients stayed longer in ICU with mean NLR 2.9 (Table 7), compared to 41 who did not. The mean NLR in these patients were 2.8 and 1.8, respectively.

Table 7: ICU stay with mean NLR

ICU	N	Mean NLR
1 (>3days)	96	2.7914
2 (<3 days	41	1.8300

4.4. Prolonged hospital/ ward stay (>7 days)

Seventy-one patients stayed more than 7 days in hospital/ ward and the mean NLR in this group was 2.9 (Table 8).

Table 8: Hospital/ ward stay with mean NLR

Hospital/ ward stay	N	Mean NLR
1 (>7days)	71	2.9421
2 (<7 days	66	2.0320

There is significant difference ($p<0.01$) in prolonged ICU and hospital/ ward stay when NLR is 2.5 and more, were compared to NLR less than 2.5. 44 patients stayed more than 3 days in ICU when NLR 2.5 and more, compared to 52 patients who had NLR < 2.5. 34 (70.8%) patients with NLR $\geq$ 2.5, had prolonged hospital/ ward stay compared to 37 (41.6%) patients who had NLR< 2.5 (Table 9).

Table 9: Prolonged ICU and hospital/ ward stay according to NLR

	Prolonged ICU stay		Prolonged hospital/ ward/ ward stay		
	n	%	n	%	
NLR <2.5 (n=89)	52	58.40%	37	41.60%	p<0.001
NLR $\geq$2.5 (n=48)	44	91.70%	34	70.80%	
Total	96		71		

5.0 Discussion

There were 260 CABG performed at our institution from 2013 until 2017. However, only 137 cases fulfilled all the criteria for the study because although complete blood count (CBC) is a compulsory pre-operative investigation, white cell differential count is not. Thus, NLR was not available in the remaining 123 patients. Most of our patients were Malays, which reflects the local population. Males constituted the majority (79.5%) of patients, which is consistent with other studies on coronary artery diseases (A.H.E.M. Maas, 2010). Females usually present with CAD at a later age compared to the males. This is due to the cardiovascular protection provided by the female sex hormones, until menopause. However, this could also mean that women are less investigated for the presence of CAD (Khairudin, 2012).

A few studies were done to define the normal value for NLR. However, so far, no consensus on normal NLR value is available. A Korean study reported mean NLR in healthy patients to be 1.65 (1.63 in men and 1.66 in women) (Jeong Soo Lee, 2018). Some studies recommended different cut-off values as a predictive tool in different diseases. Kamal et al. reported a cut-off value for NLR to be 2.13, for diagnosis of CAD in Western Indians (Kamal Sharma, 2017). Arbel et al. stated NLR >3 as being increased, whereas Abdullah et al. used NLR 4 as a cut-off value to predict outcome in post-CABG patients in Turkey. Bajin et al. used NLR cut-off value of 3 as a prognostic tool in breast cancer (Bajin Wei, 2016). In stage III melanoma, NLR $\geq$ 2.5 was shown to be a strong predictor for disease recurrence (Junjie Ma, 2018). In this study, we used NLR $\geq$2.5 as the cut-off and thus should correlate with worse prognosis in patients after CABG. Analysis of our results also showed that the mean NLR in our sample population is 2.5 ($\pm$ 2.8, CI: 95%; 0.81 – 11.44). We could probably use a higher cut-off value or a few cut-off values to assess the association with outcome parameters and risk factors.

5.1 Association of NLR with Risk Factors

WHO classified overweight as BMI more than 25 kg/m^2. However, few studies recommended different classification a for Asians because they have a higher risk of developing comorbidities such as cardiovascular diseases and T2DM at BMI<25kg/m^2 (Jeong Uk Lim, 2017). Thus, WHO expert consultation identified four potential public health points (23.0, 27.5, 32.5, and 37.5 kg/m^2) for Asian populations (WHO Expert Consultation, 2004). In this study, we used the WHO classification of weight status (Table 3).

There is no difference in the mean NLR of patients who were smokers and non-smokers, overweight (or BMI ≥25) and had normal BMI or hypertensive. However, the difference is significant in T2DM. A study by Mazhar H. et al. reported that increased NLR is associated with increased HbA1c and poor glycaemic control in patients with T2DM (Mazhar Hussain, 2017). The author stipulated the presence of ongoing inflammation and diabetes complications would contribute to elevated NLR. We did not include any information on the presence of diabetic complications or glycaemic control in the T2DM patients. However, we excluded all cases with known inflammatory diseases and acute inflammation pre-operatively.

5.2 Prolonged ICU and hospital/ ward stay

Post- CABG morbidity is relatively high compared to perioperative mortality. Complications associated with CABG may be attributed to inflammatory changes that occur during extracorporeal circulation (Abdullah Ozer, 2018). The study by Ozer et al. also showed prolonged ICU and hospital stay in patients with NLR higher than 4. Our results showed a significant difference ($p< 0.05$) in the prolonged ICU and hospital/ ward stay when comparing patients with NLR<2.5 and NLR ≥2.5. Prolonged ICU stay is an undesirable outcome because it prevents the use of ICU facilities by other patients and increases the cost of hospital care (Tunc M, 2018). The author reported the use of intra-aortic balloon pump, use of ≥ 2 inotropic agents, the presence of post-operative myocardial infarction and the need for post-operative haemodialysis as factors contributing to prolonged ICU stay. A Brazilian study reported prolonged ICU to stay in 22.1%, and prolonged ward stay (defined as >7 days) in 27.9%, of post-CABG patients (Elayne Kelen de Oliveira, 2013). Diabetes and smoking were reported as predictors of ICU outcome, while ejection fraction <50% as a predictor of ward outcome. A Malaysian study reported 50% of post CABG patients stayed more than 14 days in hospital/ ward and the author identified diabetes and wound infection as independent factors that contributed to prolonged hospital/ ward stay (Khairudin, 2012).

Inflammation is known to cause atherosclerosis, and other chronic diseases such as cancer, connective tissue disease and chronic renal failure. A study by Jagadish H.R. et al. showed that patients with abnormal coronary artery angiography (CAG) had significantly higher NLR compared to patients with normal CAG, which correlates with severity of CAD ((Jagadish H. R., 2018). A more severe CAD would place the patient at a higher risk of getting complications to post CABG. A higher neutrophil count is associated with an increased risk of death, as would lymphopenia. The risk seems to be increased when the balance between neutrophils and lymphocytes is lost. Neutrophils were shown to contribute to atherosclerosis and plaque instability through different inflammatory mediators (Basem Azab, 2013).

6.0 Conclusion and recommendation

NLR is a useful and inexpensive inflammatory marker which is shown to be associated with poor outcome in post CABG patients. Preoperative NLR is significantly higher in patients who had prolonged ICU and hospital/ ward stay and T2DM. Both outcomes would affect the quality of life in post CABG patients. A standard normal cut-off value of NLR should be made available before NLR can be used in clinical setting.

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References

Abdullah, O., Barış, M., Yiğit, K., Levent, O., Erkan, İ., Mustafa, A., Yusuf, U., & Metin, A. (2018). The effect of neutrophil-lymphocyte ratio on the postoperative course of coronary artery bypass graft surgery. *Turkish Journal of Medical Sciences, 48*, 1036-1040.

Arbel, Y., Finkelstein, A., Halkin, A., Birati, E.Y., Revivo, M., Zuzut, M., Shevach, A., Berliner, S., Herz, I., & Keren, G., Banai, S. (2012). Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. *Atherosclerosis, 225*(2), 456-460. doi:10.1016/j.atherosclerosis.2012.09.009.

Azab, B., Shariff, M.A., Bachir, R., Nabagiez, J.P., & McGinn, J.T.Jr. (2013). Elevated preoperative neutrophil/ lymphocyte ratio as a predictor of increased long-term survival in minimal invasive coronary artery bypass surgery compared to sternotomy. *Journal of Cardiothoracic Surgery, 8*, 193. doi: 10.1186/1749-8090-8-193.

Balta, S. et al. (2016). The Relation Between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. *Clinical and Applied Thrombosis/Hemostasis, 22*(5), 405-411.

Bhat, T., Telly, S., Rijal, J., Bhat, H., Raza, M., Khoueiry, G., Meghani, M., Akhtar, M., Costantino, T. (2013). Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Revew of Cardiovascular Therapy, 11*(1), 55-59.

Bhutta, H., Agha, R., Wong, J., Tang, T. Y., Wilson, Y. G., & Walsh, S. R. (2011). Neutrophil-Lymphocyte Ratio Predicts Medium-Term Survival Following Elective Major Vascular Surgery: A Cross-Sectional Study. *Vascular and Endovascular Surgery, 45*(3), 227-231. Retrieved from https://journals.sagepub.com/doi/abs/10.1177/1538574410396590.

Boudi, F.B., Ali, Y.S. (2016). Coronary Artery Atherosclerosis. Retrieved from https://emedicine.medscape.com/article/153647-overview

Dal Boni, A.L.M., Martinez, J.E., & Saccomann, I.C.R.S. (2013). Quality of Life of patients undergoing coronary artery bypass grafting. *Acta Paulista de Enfermagem, 26*(6), 575-580. Retrieved from https://dx.doi.org/10.1590/S0103-21002013000600011.

Fioranelli, M., Bottaccioli, A.G., Bottaccioli, F., Bianchi, M., Rovesti, M., Roccia M.G. (2018). Stress and Inflammation in Coronary Artery Disease: A Review Psychoneuroendocrineimmunology-Based. *Frontiers in Immunology, 9*, 2031. doi:10.3389/fimmu.2018.02031.

Fowler A.J., Agha R.A.(2013). Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography: The growing versatility of NLR. *Atherosclerosis, 228*(1), 44-45.

Henderson, A. (1996). Coronary heart disease: Overview. *The Lancet, 348(Special Issue)*, S1-S4. doi:10.1016/S0140-6736(96)98001-0

Horne, B.D., Anderson, J.L., John, J.M., Weaver, A., Bair, T.L., Jensen, K.R., Renlund, D.G., Muhlestein, J.B.; Intermountain Heart Collaborative Study Group. (2005). Which White Blood Cell Subtypes Predict Increased Cardiovascular Risk? *Journal of the American College of Cardiology, 45*(10),1638-1643. doi:10.1016/j.jacc.2005.02.054

Hussain, M., Babar, M.Z.M., Akhtar, L., Hussain, M.S. (2017). Neutrophil lymphocyte ratio (NLR): A well assessment tool of glycaemic control in type 2 diabetic patients. *Pakistan Journal of Medical Sciences, 33*(6), 1366-1370. doi:10.12669/pjms.336.12900.

Jagadish, H. R., Divyaprakash, M., Manjunath, R., & Girish, P.G. (2018). Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. *International Journal of Advances in Medicine, 5*(2), 265-270. Retrieved from https://www.ijmedicine.com/index.php/ijam/article/view/989.

Khairudin, Z. (2012). Determinants of Prolonged Stay After Coronary Artery Bypass Graft Surgery. *Procedia Social and Behavioral Sciences, 36*, 87-95.

Kulik, A. (2017). "Quality of life after coronary artery bypass graft surgery versus percutaneous coronary intervention: what do the trials tell us?", *Current Opinion in Cardiology, 32*(6), 707-714. doi:10.1097/HCO.0000000000000458.

Lee, J.S., Kim, N.Y., Na, S.H., Youn, Y.H., & Shin, C.S.. (2018). Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine, 97*(26): e11138. doi: 10.1097/MD.0000000000011138.

Lie, I., Arnesen, H., Sandvik, L., Hamilton, G., & Bunch, E.H. (2010). Predictors for Physical and Mental Health 6 Months After Coronary Artery Bypass Grafting A Cohort Study. *European Journal of Cardiovascular Nursing, 9*(4), 238-43. doi:10.1016/j.ejcnurse.2010.02.001.

Lim, J.U., Lee, J.H., Kim, J.S., Hwang, Y.I., Kim, T.H., Lim, S.Y., Yoo, K.H., Jung, K.S., Kim, Y.K., Rhee, C.K. (2017). Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. *International Journal of Chronic Obstructive Pulmonary Disease, 12*, 2465–2475. doi: 10.2147/COPD.S141295.

Ma, J., Kuzman, J., Ray, A., Lawson, B.O., Khong B., Xuan, S., Hahn, A.W., & Khong, H.T. (2018). Neutrophil-to-lymphocyte ratio (NLR) as a predictor for recurrence in patients with stage III melanoma. *Scientific Reports, 8*(1), 4044.

Maas, A.H.E.M., & Appelman Y.A. (2010). Gender differences in coronary heart disease. *Netherlands Heart Journal, 18*(12), 598-602.

Oliveira, E.K., Turquetto A.L., Tauil, P.L., Junqueira, L.F. Jr., & Porto, L.G. (2013). Risk factors for prolonged hospital/ ward stay after isolated coronary artery bypass grafting. *Brazilian Journal of Cardiovascular Surgery, 28*(3), 353-63. doi: 10.5935/1678-9741.20130055.

Ross, R. (1999). Atherosclerosis: an inflammatory disease. *New England Journal of Medicine, 340*(2), 115-126. doi:10.1056/NEJM199901143400207.

Rumsfeld, J.S., Ho, P.M., Magid, D.J., McCarthy, M. Jr., Shroyer, A.L., MaWhinney, S., Grover, F.L., & Hammermeister, K.E. (2004). Predictors of health-related quality of life after coronary artery bypass surgery. *The Annals of Thoracic Surgery, 77*(5), 1508–1513. doi: https://doi.org/10.1016/j.athoracsur.2003.10.056

Sayols-Baixeras, S., Lluís-Ganella, C., Lucas, G., & Elosua, R. (2014). Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants. *The Application of Clinical Genetics, 7*, 15–32. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3920464/. doi:10.2147/TACG.S35301

Sharma, K, Patel, A.K, Shah, K.H., & Konat A. (2017). 'Is Neutrophil-to-Lymphocyte Ratio a Predictor of Coronary Artery Disease in Western Indians?", *International Journal of Inflammation*, *vol. 2017*. Article ID 4136126, 8 pages. Retrieved from https://doi.org/10.1155/2017/4136126.

Tunç, M., Şahutoğlu, C., Karaca, N., Kocabaş, S., & Aşkar, F.Z. (2018). Risk factors for prolonged ICU stay after open heart surgery in adults. *Turkish Journal of Anaesthesiology and Reanimation, 46*(4), 283-291. doi: 10.5152/TJAR.2018.92244.

Vincelj,,J. Bitar, L., Jendričko, T., Udovičić, M., & Petrovečki, M. (2015). Health-related quality of life five years after coronary artery bypass graft surgery. *International Journal of Cardiology, 182*, 68-69. doi:10.1016/j.ijcard.2014.12.106

Wayne A.R. (1994). Inflammation and Coronary Artery Disease. *New England Journal of Medicine*, *331*, 468-469. doi:10.1056/NEJM199408183310709

Wei, B., Yao M., Xing, C., Wang, W., Yao, J., Hong, Y., Liu, Y., & Fu, P. (2016). The neutrophil lymphocyte ratio is associated with breast cancer prognosis: an updated systematic review and meta-analysis. *Oncology Targets and Therapy, 9*, 5567-5575. doi: 10.2147/OTT.S108419

World Health Organization Expert Consultation (2004, January 10). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet, 363*(9403),157-63. Erratum in (2004 Mar 13) *Lancet; 363*(9412),902. doi:10.1016/S0140-6736(03)15268-3.