



RESEARCH ARTICLE

Neutrophil Lymphocyte Ratio as a predictor of systemic inflammation - A cross-sectional study in a pre-admission setting. [v1; ref status: indexed, <http://f1000r.es/5cy>]

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Abstract

Background: Neutrophil:lymphocyte ratio (NLR) is an emerging biomarker that is used to predict postoperative mortality and morbidity in cardiac and cancer surgeries. The association of this biomarker with systemic illness and its usefulness in risk assessment of preoperative patients has not been fully elucidated.

Objectives: To determine the prevalence of elevated NLR in preoperative patients and to examine the relationship between elevated NLR and the presence of systemic illnesses as well as anaesthesia risk indices such as American Society of Anesthesia (ASA) and the revised cardiac risk index (RCRI) scores.

Design: Cross-sectional study

Setting: Anaesthesia pre-admission clinic, Toronto Western Hospital, Toronto, Canada

Patients: We evaluated 1117 pre-operative patients seen at an anesthesia preadmission clinic.

Results: NLR was elevated (>3.3) in 26.6% of target population. In multivariate analysis, congestive cardiac failure, diabetes mellitus and malignancy were independent risk factors predicting raised NLR. After regression analysis, a relationship between NLR and ASA score (Odds Ratio 1.78; 95% CI: 1.42-2.24) and revised cardiac risk index (RCRI, odds ratio 1.33; 95% CI: 1.09-1.64, p-value: 0.0063) was observed.

Conclusions: NLR was elevated (> 3.3) in 26.6% of patients. Congestive cardiac failure and malignancy were two constant predictors of elevated NLR at >3.3 and > 4.5. There was a strong association between NLR and anesthesia risk scoring tools of ASA and RCRI.

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Introduction

Perioperative major cardiovascular adverse events contribute to significant morbidity and mortality in patients undergoing non-cardiac surgery¹. Prospective identification of high risk patients coming for surgery will allow hospitals to prioritise the allocation of valuable resources such as intensive care beds and to avoid unplanned readmissions². The use of the American Society of Anaesthesia (ASA) physical status as the sole risk stratification score may not give the complete picture of the patient's underlying inflammatory processes and may be inadequate for identifying risk during the immediate postoperative period. Hence, in addition to risk indices, biomarkers may have a role in assisting risk prediction and aid in developing a management plan. Biomarkers such as B-natriuretic peptide and C-reactive peptide have been effectively used in the past to stratify risk and optimise patient care to minimise the adverse events in the perioperative setting³⁻⁶. However, these markers have some limitations in their role in routine clinical practice, as they have been shown to provide either modest or no improvement over conventional risk factors in predicting cardiovascular outcome in non-heart failure populations³.

An ideal biomarker would be something that can be measured or derived from routine blood work done during the preoperative preparation of the patient for the surgery. It should also have a high predictive value for the risk factors of interest. The role of white cell counts in predicting cardiac morbidity and mortality after surgery is well recognised⁷⁻⁹. An elevated neutrophil count has been shown to correlate with worse outcomes in patients with acute coronary events¹⁰.

Neutrophil:lymphocyte ratio (NLR), a ratio of the neutrophil to lymphocyte count, has recently been shown to be predictive of morbidity and mortality in patients with acute coronary syndrome^{11,12}. In addition, elevated NLR is associated with increased in-hospital and post-hospital mortality as well as increased risk in myocardial infarction patients¹³⁻¹⁵. However, the role of NLR in the risk assessment of preoperative patients in the general surgical population has not been well studied, as prior studies have concentrated on specific cardiac, vascular and oncological diseases.

Therefore, we sought to study the normal values and distribution of preoperative NLR in patients before their surgery, with the primary objective of examining the prevalence of elevated NLR in the non-cardiac surgical population. Secondary objectives included examining the relationship between this biomarker and the presence of systemic illness and the anaesthesia risk indices such as the ASA physical status and the RCRI scores¹⁶.

Methods

Ethical approval for this study was provided by the University Health Network Research Ethics Board, Toronto, Canada on 26th May 2013 (Protocol#: 13-6395; REB Co-chair: Anna Gagliardi). Informed consent was waived by the REB for this study. This study complies with STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statements for reporting of observational trials¹⁷.

This cross-sectional study investigated all consecutive elective surgical patients who attended the anaesthesia pre-admission clinic at our institution from 1st January 2013 to 30th April 2013. The

pre-admission clinic conducts preoperative preparation and anaesthetic evaluation of patients undergoing major orthopedic, neuro-, spine, bariatric and general surgeries. Orthopedic surgeries included knee or hip joint replacements, hand and foot surgeries; neurosurgery included craniotomies for tumors, clipping of aneurysms and transphenoidal pituitary surgeries; spinal surgeries included lumbar and cervical decompression and fusions and tumor resections, and general surgeries included bowel resections, hernia repairs and Roux en Y gastric bypasses.

All patients in this cohort who were eligible for a complete blood count test were included in this study. As per the hospital policy, all patients who were above 60 years of age or suspected of having anemia, or if they required a cross-matching for the surgical procedure, will undertake a complete blood count test. Patients who are not required to have this blood test preoperatively and those with incomplete blood test results were excluded from the study.

As per our clinic's practice, all major surgical patients are assessed by a nurse, and clinical history and examinations are entered in an electronic 'Clinical Anaesthesia Information System' (CAIS). The data were identified retrospectively from the CAIS database and extracted for patients demographics (age, sex), anaesthetic variables (ASA status), surgical variables (type of surgery) and presence of systemic illness medications (number of medications, ischemic heart disease, congestive cardiac failure, hypertension, diabetes, chronic kidney disease, cerebrovascular disease, and oncological disease). RCRI was computed based on the variables obtained from the clinical database. The differential white blood cell count, containing the neutrophil and lymphocyte absolute counts, and platelet counts were retrieved separately from the hematology records in the hospital's electronic patient record (EPR). NLR was calculated from the complete blood counts.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD). Categorical data were summarised using absolute values (percentage). Previous studies have shown that an NLR value of > 3.3 and > 4.5 was shown to predict increased risk of myocardial infarction in post-surgical and asymptomatic populations, respectively^{12,13}. Hence we selected both cut-off values for dichotomous comparisons to categorise patients into normal or elevated NLR.

Welch's t-test was used for comparison between groups for continuous variables. Effects of the different variables on NLR were calculated in univariate analysis. The candidate predictors for the multivariate model were selected by screening with univariate analysis with a threshold for inclusion of $p < 0.25$. Multiple logistic regressions were used to determine independent predictors for elevated NLR. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using R (Version 3.02, The Comprehensive R Archive Network; <http://cran.r-project.org>, Accessed 17th November 2014).

Results

Data sampling

One thousand, one hundred and seventy-three patients were identified through the CAIS database. Fifty-six patients were excluded

from the study as there was either no complete blood count performed or the white cell count subtypes were not performed. Therefore, 1117 patients were included for further analysis.

The patient population had a mean (\pm SD) age of 59 (\pm 14.9) years and was comprised of 54.3% females. The majority of patients had an ASA score of 2 or 3 (91.6%). Patients for orthopedic surgery were the largest group seen in the pre-admission clinic (44.0%), followed by neurosurgery (21.5%), spinal surgery (15.4%), bariatric

surgery (7.9%) and the rest (11.2%) were for urology and general surgery.

Baseline characteristics of patients grouped according to NLR > 3.3 and NLR > 4.5 are summarised in [Table 1](#). The median value of NLR in the study population was 2.20. About one fourth (26.6%) of patients had a NLR value > 3.3 and 9.04% patients had a NLR value > 4.5. In univariate analysis using NLR > 3.3 as a threshold, age, congestive cardiac failure, chronic kidney disease, malignancy

Table 1. Characteristics of patients with NLR thresholds > 3.3 and > 4.5.

Characteristic	<=3.3	>3.3	<=4.5	>4.5
N	882(79)	235(21)	1016(90.9)	101(9.1)
Mean Age (SD)	58 (14.63)	62 (15.44)	59 (14.79)	63 (15.82)
Female	487(55.2)	119(50.6)	561(55.2)	45(44.6)
ASA1	43(4.9)	6(2.6)	47(4.6)	2(2.0)
2	411(46.6)	77(32.8)	464(45.7)	24(23.8)
3	405(45.9)	141(60.0)	478(47.0)	68(67.3)
4	23(2.6)	11(4.7)	27(2.7)	7(6.9)
5	0(0.0)	0(0.0)	0(0.0)	0(0.0)
IHD	98(11.1)	33(14.0)	115(11.3)	16(15.8)
CHF	28(3.2)	21(8.9)	36(3.5)	13(12.9)
HT	404(45.8)	119(50.6)	474(46.7)	49(48.5)
Diabetes	141(16.0)	41(17.4)	162(15.9)	20(19.8)
CV	37(4.2)	12(5.1)	46(4.5)	3(3.0)
Malignancy	87(9.9)	40(17.0)	109(10.7)	18(17.8)
CKD Stage:1	423(48.3)	71(30.3)	466(46.2)	28(28.0)
2	207(23.7)	62(26.5)	244(24.2)	25(25.0)
3	80(9.1)	43(18.4)	102(10.1)	21(21.0)
4	6(0.7)	3(1.3)	8(0.8)	1(1.0)
5	6(0.7)	4(1.7)	8(0.8)	2(2.0)
Medications :0	252(28.6)	47(20.0)	279(27.5)	20(19.8)
1	308(34.9)	82(34.9)	362(35.6)	28(27.7)
2	167(18.9)	52(22.1)	195(19.2)	24(23.8)
3	106(12)	33(14)	123(12.1)	16(15.8)
4	36(4.1)	16(6.8)	43(4.2)	9(8.9)
5	10(1.1)	4(1.7)	11(1.1)	3(3)
6	2(0.2)	1(0.4)	2(0.2)	1(1)
RCRI :0	634(71.9)	147(62.6)	718(70.7)	63(62.4)
1	193(21.9)	66(28.1)	232(22.8)	27(26.7)
2	43(4.9)	11(4.7)	50(4.9)	4(4.0)
3	10(1.1)	7(3.0)	12(1.2)	5(5.0)
4	2(0.2)	3(1.3)	3(0.3)	2(2.0)
5	0(0.0)	1(0.4)	1(0.1)	0(0.0)

Data layout: Numbers of patients (percentage of the total cohort). **Key:** ASA - American Society of Anaesthesiologist physical status score; IHD - Ischemic heart disease; CHF - Congestive heart failure; HT - Hypertension; CV - Cerebral Vascular; CKD stage 1-5 - Chronic kidney disease stage 1-5; RCRI- Revised Cardiac Risk Index Score.

and the number of prescribed medications were increasingly associated. Congestive cardiac failure, diabetes mellitus and malignancy were the independent risk factors associated with elevated NLR after multivariate analysis (Table 2).

However, when NLR > 4.5 were analyzed, polypharmacy emerged as a risk factor along with congestive cardiac failure and malignancy (Table 3). Diabetes mellitus was not an independent risk factor.

In addition, NLR was significantly elevated in patients with any type of malignancy compared to patients with no malignancy (mean NLR 3.42 vs 2.70, $p = 0.049$). Regression analysis showed a strong association between NLR and ASA scores (Odds Ratio 1.78; 95% CI: 1.42-2.24, p -value: <0.001) and also between NLR and RCRI (Odds Ratio 1.33; 95% CI: 1.09-1.64, p -value: 0.0063).

Dataset 1. Neutrophil-lymphocyte ratio study - patient characteristics, co-morbidities, revised cardiac risk index, ASA status and NLR

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For Gender - 1: male, 0 - female; Type of Surgery: 1: Orthopedic, 2: Neurosurgery, 3: Spinal, 4: Bariatric, 5: Gen Surg/Colorectal, 6: Urological, 7: Others; BMI: 0: < 30, 1: 30-39.9, 2: > 40; For Comorbid conditions: 1: yes, have disease, 2: no disease; For smoking status: 0: Never smoked, 1: Previous or current smoker; For Chronic Kidney Disease Stage: 1 = eGFR > 90, 2 = 60-89, 3 = 30-59, 4 = 15-29, 5 = < 15 or in renal therapy;

For all medications (except HT meds): 1 = yes, takes medications, 2 = no medications; For HT meds: the number of medications; For RCRI - Revised Cardiac Risk Index²⁹

Table 2. Results of univariate and multivariate logistic regression models for neutrophil lymphocyte ratio (NLR > 3.3).

Logistic regression Variable	Univariate		Multivariate	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.004
Gender	1.20 (0.90-1.60)	0.211	1.16 (0.86-1.57)	0.343
IHD	1.31 (0.85-1.99)	0.218	0.95 (0.60-1.52)	0.836
CHF	2.99 (1.66-5.37)	0.0002	2.28 (1.21-4.31)	0.011
HT	1.21 (0.91-1.62)	0.187	0.87 (0.60-1.25)	0.439
Diabetes	1.11 (0.76-1.63)	0.59	0.83 (0.52-1.32)	0.43
CV disease	1.23 (0.63-2.40)	0.545	0.94 (0.46-1.89)	0.855
CKD	1.25 (1.09-1.45)	0.002	1.05 (0.89-1.23)	0.599
Malignancy	1.90 (1.37-2.64)	0.0001	1.79 (1.28-2.50)	0.001
Number of Medications	1.18 (1.06-1.32)	0.003	1.13 (0.96-1.33)	0.134

Key: OR - odds ratio; CI - confidence interval; IHD - Ischemic heart disease; CHF - Congestive heart failure; HT - Hypertension; CV - Cerebral Vascular; CKD - Chronic kidney disease.
Significant results in bold face.

Table 3. Results of univariate and multivariate logistic regression models for neutrophil lymphocyte ratio (NLR > 4.5).

Logistic regression Variables	Univariate		Multivariate	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.02 (1.00-1.03)	0.03	1.01 (0.99-1.03)	0.20
Gender	1.53 (1.02-2.32)	0.04	1.42 (0.92-2.20)	0.11
IHD	1.47 (0.83-2.60)	0.18	0.89 (0.47-1.70)	0.72
CHF	4.02 (2.05-7.86)	<0.01	2.86 (1.34-6.10)	<0.01
HT	1.08 (0.72-1.62)	0.72	0.62 (0.36-1.06)	0.08
Diabetes	1.30 (0.78-2.18)	0.31	0.73 (0.37-1.42)	0.35
CV disease	0.65 (0.20-2.11)	0.47	0.41 (0.12-1.43)	0.16
CKD stage	1.25 (1.03-1.52)	0.03	1.03 (0.81-1.30)	0.83
Malignancy	2.41 (1.63-3.56)	<0.01	2.26 (1.50-3.41)	<0.01
Number of medications	1.30 (1.12-1.51)	0.0006	1.40 (1.11-1.76)	<0.01

Key: OR - odds ratio; CI - confidence interval; IHD - Ischemic heart disease; CHF - Congestive heart failure; HT - Hypertension; CV - Cerebral Vascular; CKD - Chronic kidney disease.
Significant results in bold face.

Discussion

To our knowledge this is the first cross-sectional study on the prevalence of elevated NLR in a preoperative setting. In our patient population, 26.6% of patients had an elevated NLR value of more than 3.3, which had been shown to be associated with increased mortality after cardiac surgery¹⁸. We found an independent association between congestive cardiac failure and NLR values > 3.3 and > 4.5. This is in line with established evidence on the utility of NLR in predicting long-term outcome in acutely decompensated heart failure¹⁹. Our study also showed a strong association between the presence of malignancy and NLR thresholds of > 3.3 and > 4.5. This confirms the previously known prognostic value of NLR in terms of mortality and recurrence of disease in patients with cancer²⁰.

In addition, we found a significant association between NLR and ASA physical status and RCRI. This raised the possibility that NLR may be of added value in anaesthetic risk stratification and comparison in a preoperative setting. This may be particularly relevant in a tertiary hospital setting where patients often present with many comorbidities.

Our study also showed that increased use of medication is a risk factor associated with NLR values > 4.5. The increased number of medications reflects the presence of more systemic illnesses. The relationship between polypharmacy and comorbidity is a well-recognised phenomenon especially in the elderly²¹. This also highlights the relationship between NLR and presence of increased disease burden in patients with chronic systemic illnesses.

However, we did not demonstrate an association between the presence of ischemic heart disease and elevated NLR, contrary to previous publications¹². It is not clear from our cohort the reason for this discrepancy. It may be possible that the inclusion criteria for ischemic heart disease in our database includes all patients from angina-like symptoms to patients with previous myocardial infarction, thus weakening the association between NLR and ischemic heart disease. Further, it is likely that the majority of patients who presented to the pre-surgical clinic had stable ischemic heart disease and are on statin therapy and therefore have suppression of low-grade inflammation, leading to a lower NLR than anticipated.

Prediction of systemic illness and its severity are crucial in formulating a safe intraoperative plan and postoperative care in surgical patients. Elevated NLR is known to predict all-cause mortality in cardiac and major vascular surgeries^{18,22}. Elevated preoperative NLR is also associated with increased morbidity postoperatively, with prolonged hospitalization and increased intensive care admission¹⁸. Further, elevated NLR is associated with increased morbidity and mortality in sepsis²³. Hence, the use of NLR as a potential biomarker for preoperative risk assessment and stratification can be pertinent for several reasons. Firstly, NLR is obtained from a complete blood count that is routinely performed pre and postoperatively; it doesn't necessitate additional investigation and is an inexpensive and readily available marker. Secondly, the application of elevated NLR can be used to plan for the postoperative support and rehabilitation of patients undergoing major surgeries. Another

similar finding has been observed in the general population cohort in the recently published post-hoc analysis of the National Health and Nutrition Examination Survey-III that showed that NLR can independently predict cardiac mortality. In analysis of 7363 subjects, Shah *et al.* showed that NLR can be used as a risk index to reclassify patients from low to intermediate risk categories and improve the Framingham risk score²⁴.

Elevated NLR has been shown to be associated with increased tumor necrosis factor (TNF) alpha, and various interleukins (IL-6, IL-7, IL-8, IL-12, IL-17)^{25,26}. These markers are known to be associated with poor outcome in critically ill patients, as well as with increased incidence of recurrent ischemic events in cardiac patients^{27,28}. However, measuring these biomarkers is expensive and tests are not routinely performed. In contrast, NLR is a simple index derived from routine blood tests which might provide equal and valuable information in the preoperative setting.

Our study suffers from some major limitations. This study is not designed to examine the utility of this biomarker for stratifying risk and predicting clinical end-points of mortality and major cardiovascular adverse events. Rather it is designed to provide a cross-sectional "snapshot" of the distribution of NLR in a cohort of patients who attended the anaesthesia pre-admission clinic before their surgery and to correlate this biomarker with the presence of systemic illnesses.

Further prospective cohort studies are needed to examine the optimal role of NLR as a biomarker in the perioperative setting. Establishing a relationship between the NLR and systemic illnesses in elective preoperative patients sets the stage for evaluating the role of this biomarker in future prospective studies looking at the ideal cut-off value of these biomarkers and the correlation between elevated NLR, and perioperative morbidities and mortalities. Prediction of systemic illness and its severity are crucial in formulating a safe intraoperative plan and postoperative care in surgical patients.

Conclusion

In summary, elevated preoperative NLR (> 3.3) was observed in 26.6% of patients attending a pre-surgical anaesthetic clinic at our tertiary hospital. Congestive cardiac failure and malignancy were two constant associations of elevated NLR at > 3.3 and > 4.5 respectively. There was also a strong association between NLR, and ASA and RCRI scores of patients. More studies are needed to determine the utility of NLR as a biomarker in the preoperative risk stratification of patients.

Data availability

F1000Research: Dataset 1. Neutrophil-lymphocyte ratio study - patient characteristics, co-morbidities, revised cardiac risk index, ASA status and NLR., [10.5256/f1000research.6474.d47345](https://doi.org/10.5256/f1000research.6474.d47345)²⁹

Author contributions

TPT contributed to the study design and assisted in data collection and analysis of the data. JM and AA contributed to data collection.

APG contributed to the study design. ES assisted with the data analysis. LV contributed the study concept, content data collection and analysis. All authors were involved in writing the manuscript and have agreed to its final content.

Competing interests

No competing interests were disclosed.

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Referee Report 13 July 2015

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Edwin Seet

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Dr Venkatraghavan and colleagues have undertaken a cross-sectional observation study in a tertiary centre in Toronto, evaluating the utility of a raised Neutrophil:Lymphocyte Ratio as a biomarker for risk stratification in the perioperative period. A raised NLR was compared with conventionally accepted risk assessment tools such as the ASA physical status and the RCRI scores. Multivariate regression analysis was done to investigate independent predictors of a raised NLR. The authors found that a raised NLR was associated with malignancy, congestive heart failure and polypharmacy. A relationship between raised NLR and 2 cutoffs and increased ASA physical status and RCRI scores was observed.

Several possible opportunities of improvement of the manuscript may exist:

1. This is a novel study investigating raised NLR and perioperative comorbidities and conventional risk stratification tools. Most readers would not be familiar with the biological plausibility of a raised NLR and perioperative outcomes. More details may be included in the introduction and discussion to make this clearer to the readers.
2. Dr Peter Nagele and colleagues published a landmark paper correlating a raised High-Sensitivity Troponin T test and perioperative outcomes in [Nagele *et al* \(2013\)](#). This publication should be referenced together with other biomarkers in the introduction and discussion such as the BNP and CRP.
3. The authors have chosen to represent the association between NLR and ASA physical status and RCRI scores in the form of Odds Ratio. I wonder if correlation statistics and/or Receiver Operating Characteristics at various cutoffs may be utilized and represented in the results as well?

All in all, Dr Venkatraghavan *et al* have undertaken an interesting study which answers a novel and fairly important clinical question. I would like to congratulate them on a stellar effort.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Referee Report 03 June 2015

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**Neeraj N. Shah**

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Venkatraghavan et al present an interesting study of preoperative neutrophil to lymphocyte ratio (NLR) in patients undergoing non-cardiac surgeries. While NLR has been studied extensively in acute and chronic cardiac conditions and in the setting of cardiac surgeries, there is scarce data about NLR in non-cardiac surgeries. It is unfortunate that the authors did not look at mortality or morbidity endpoints, rather this is a cross sectional study looking at prevalence of risk factors and correlation with ASA and RCRI scores preoperatively.

Suggested revisions:

1. Introduction, first paragraph: In the sentence "Prospective identification of high risk pts..... and to avoid unplanned readmissions". How will identification of high risk preop patients avoid unplanned readmissions? This sentence is confusing and I would recommend the authors deleting the part which says "to avoid unplanned readmissions".
2. Results: Use numbers instead of words e.g. use 1,173 instead of one thousand one hundred seventy three.
3. Table 1: Please include type of surgery in table 1 (e.g. orthopedic, neurosurgery, etc.)
3. Table 1: Medications: Please lump together 4,5, or 6 medications as 4 or more medications, since the definition of polypharmacy is 4 or more medications.
4. (Major concern) Results: Table 2 clearly shows that for NLR > 3.3, the independent predictors are age, CHF and malignancy, but the authors mention CHF, DM and malignancy in the text. Kindly address this discrepancy.
4. (Major concern) Results: Number of medications: It seems that the authors conducted logistic regression with either NLR>3.3 or NLR>4.5 as the dependent variable and number of medications as an independent, **continuous** variable. This is **incorrect**. One cannot assume the number of medications to have a continuous effect. The authors need to change their analysis, and incorporate number of medications as a categorical variable with categories: zero (referent), 1, 2, 3 and 4 or more. There will be separate odds ratios for categories 1, 2, 3 and 4 or more (the authors may elect to choose different categories, but it is important that they use categories rather than a continuous variable). This may change the results, esp for NLR > 4.5.
5. (Major concern) Results: The authors need to explain in greater detail how they performed 'regression' analysis with NLR and ASA and NLR and RCRI. Was NLR treated as a continuous variable or in categories>3.3 or >4.5? What was the dependent variable? I am assuming that the authors performed logistic regression analysis with ASA or RCRI as the dependent variable and NLR as the independent variable in a continuous fashion, but this needs to be explicitly stated, since it helps in understanding what the odds ratios mean.
6. What about dividing NLR into tertiles or quartiles instead of using the said cut offs, since there are not established cut offs for NLR?
7. Discussion, first paragraph: The association that the authors observe in this study between NLR and CHF and NLR and malignancy is just that- an association. The authors cannot infer that this means that

either NLR is associated with long term outcomes in CHF (ref 19) or prognostic value of NLR in cancer (ref 20). I would therefore strongly recommend the authors to remove those two lines from the first paragraph of discussion.

8. Discussion, Third paragraph (no. of meds): This may have to be re-written after the authors re-analyze the data with no. of meds as a categorical variable.

9. The authors do have interesting findings and I was hoping to see if preoperative NLR predicts outcomes (morbidity and mortality or major cardiac events) in the postoperative period. Moreover, if NLR does predict outcomes in the postoperative period, it may be used to re-classify the existing ASA and RCRI indices for non-cardiac surgeries. The authors should mention this in discussion or conclusion as future studies that may be undertaken in this subject.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Referee Report 28 May 2015

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The authors have performed a cross sectional observational study examining the relationship between NLR, preoperative systemic illnesses and peri-operative risk markers in a large cohort of surgical patients. This makes a contribution to the existing literature by including patients from a variety of surgical specialties rather than focussing on specific surgical pathologies.

They found that increased NLR at two cut-offs was independently associated with pre-existing cardiac failure and malignancy (confirming similar findings in other studies) – but not ischaemic heart disease - in a multivariable model. Overall the design, methods and analysis are appropriate and the authors' conclusions are balanced and justified.

The study authors may consider the following points which may strengthen this work:

1. The abstract and results text state that diabetes was one of the pre-existing co-morbidities associated with increased NLR in the multivariate model, however this is not consistent with the results tables.
2. The regression models examining ASA / RCRI and NLR could be described more clearly. Were they separate univariate models or part of the wider multivariate models including co-morbidities? If the latter, the extent of co-linearity between these risk scores and the presence of co-morbidities would be useful to know.

3. As the authors point out, this study has not included clinical outcomes and did not aim to examine NLR as a prognostic marker. With this in mind, could NLR have been examined as a continuous variable in the regression model rather than being dichotomised? Dichotomising continuous data may have led to a loss of statistical power (Altman and Royston, 2006). Also, although the NLR cut-offs examined have been justified based on prior related literature, giving these cut-offs (3.3 and 4.5) might imply to the casual reader that these are prognostically important values, whereas this needs further exploration as the authors acknowledge.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
