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### Neutrophil to Lymphocyte Count Ratio as an Early Indicator of Blood Stream Infection in the Emergency Department

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Complete List of Authors:	Lowsby, Richard; Whiston Hospital, Emergency Department Gomes, Clint; Whiston Hospital, Emergency department Jarman, Ian; Liverpool John Moores University, Lisboa, Paulo; Liverpool John Moores University, Nee, Patrick; Whiston Hospital, Emergency and Critical Care Medicine; Liverpool John Moores University, Vardhan, Madhur; Whiston Hospital, Emergency Department Eckersley, Thomas; Whiston Hospital, Emergency Department Saleh, Roshan; Whiston Hospital, Emergency Department Mills, Hannah; University of Liverpool, School of Medicine
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**Neutrophil to Lymphocyte Count Ratio as an Early Indicator of Blood Stream  
Infection in the Emergency Department**

Richard Lowsby FCEM<sup>1</sup>, Clint Gomes FCEM<sup>1</sup>, Ian Jarman PhD<sup>2</sup>, Paulo Lisboa PhD<sup>2</sup>,  
Patrick Nee FCEM, FFICM<sup>1,2</sup>, Madhur Vardhan FRCPATH<sup>1</sup>, Tom Eckersley MCEM<sup>1</sup>,  
Roshan Saleh MB,ChB<sup>1</sup>, Hannah Mills MB,ChB<sup>3</sup>

- (1) Departments of Emergency and Critical Care Medicine,  
St. Helens and Knowsley Hospitals NHS Trust, Merseyside, UK  
(2) Liverpool John Moores University, Liverpool, UK  
(3) School of Medicine, University of Liverpool, UK

Author correspondence:

Professor Patrick A. Nee  
Emergency Department  
Whiston Hospital  
Merseyside L35 5DR  
United Kingdom  
Tel: +44 151 430 1853  
Fax: +44 151 430 1973  
e-mail: [patrick.nee@sthk.nhs.uk](mailto:patrick.nee@sthk.nhs.uk)

**KEY WORDS**

Infection, Bacteraemia, Emergency Department, Neutrophil to Lymphocyte Ratio

## ABSTRACT

### Objectives

Early identification of patients with blood stream infection (BSI), especially bacteraemia, is important as prompt treatment improves outcome. The initial stages of severe infection may be characterised by increased numbers of neutrophils in the peripheral blood and depression of the lymphocyte count. The neutrophil to lymphocyte count ratio (NLCR) has previously been compared with conventional tests such as C-reactive protein (CRP) and white cell count (WCC) and has been proposed as a useful marker in the timely diagnosis of bacteraemia.

### Methods

Data on consecutive adult patients presenting to the emergency department (ED) with pyrexial illness during the study period; November 2009 to October 2010, were analysed. The main outcome measure was positive blood cultures (bacteraemia). Sensitivity, specificity, positive and negative predictive values and likelihood ratios were determined for NLCR, CRP, WCC, neutrophil count (NC) and lymphocyte count (LC).

### Results

1,954 patients met the inclusion criteria. Blood cultures were positive in 270 patients, hence the prevalence of bacteraemia was 13.8%. With the exception of WCC there were significant differences in the mean value for each marker between bacteraemic and non-bacteraemic patients ( $p < 0.001$ ). The area under the receiver operating characteristic (ROC) curve was highest for NLCR (0.72;95%CI 0.69-0.75) and LC (0.71;0.68-0.74) and lowest for WCC (0.54;0.40-0.57). The sensitivity and specificity of NLCR for predicting bacteraemia were 70% (64-75%) and 57% (55-60%) respectively. Positive and negative predictive values for NLCR were 0.20 (0.18-0.23) and 0.92 (0.91-0.94) respectively. The positive likelihood ratio was 1.63 (1.48-1.79) and the negative likelihood ratio was 0.53 (0.44-0.64).

### Conclusion

Although NLCR outperforms conventional markers of infection it is insufficient in itself to guide clinical management of patients with suspected BSI, and it offers no advantage over lymphocyte count. However, it may offer some diagnostic utility when taken into account as part of the overall assessment.

**INTRODUCTION**

The incidence of bacteraemia, defined as the presence of viable bacteria in the bloodstream, in patients admitted to hospital is approximately one per cent. The mortality rate is 25-30%, increasing to 50% when associated with severe sepsis.[1] Patients with blood stream infection (BSI) have worse outcomes than matched culture-negative controls, and early treatment improves the outcome.[2,3] Fever is common in patients presenting to the emergency department (ED), but BSI is confirmed in only a small minority. The presence or absence of infection cannot be confirmed at initial presentation.[4] It would be inappropriate to draw blood for culture in every case and scores have therefore been derived that may improve the yield of positive results. [5]

A variety of physical and biochemical markers are available to the clinician but all have limitations. Clinical features such as the systemic inflammatory response syndrome (SIRS) criteria and the Shapiro score are sensitive indicators of bacteraemia but lack specificity.[5,6,7] Currently available laboratory investigations include the white cell count (WCC) and C-reactive protein (CRP). However, up to 50% of patients with bacteraemia may exhibit a normal WCC, and CRP adds little value over and above the neutrophil count (NC) and lymphocyte count (LC).[8,9] Procalcitonin (PCT) has been used to guide antibiotic stewardship in critical care but evidence for its use in the ED setting is limited.[10]

The neutrophil lymphocyte count ratio (NLCR)

The early hyper dynamic phase of infection is characterised by a pro-inflammatory state mediated by neutrophils, macrophages and monocytes with release of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-alpha) and interleukins 1 and 6. This systemic inflammatory response is associated with suppression of neutrophil apoptosis, which augments neutrophil-mediated killing as part of the innate response but may also cause tissue injury.[11] At the same time

lymphocyte apoptosis is increased in the thymus and spleen. This can lead to immune system suppression, multi-organ dysfunction and death.[12]

NLCR is a measure of systemic inflammation [13] and it has been used as a guide to prognosis in community acquired pneumonia[14], ischaemic heart disease[15] and cancer.[16]

NLCR is easily calculated and is immediately available from the full blood count as part of a panel of investigations routinely ordered in admitted patients. Its use in the ED setting could afford the earliest opportunity to identify patients at risk of BSI and the timely administration of antimicrobials.

De Jager et al evaluated the performance of NLCR and other markers of infection in predicting bacteraemia in adults presenting to a Dutch ED.[17] A cohort of 92 patients with suspected community acquired bacteraemia and subsequent positive blood cultures were compared with 92 age and sex matched controls with negative blood cultures. There was no significant difference in WCC and NC between the two groups. However, the infected group had significantly lower LC and significantly higher CRP and NLCR. The area under the ROC curve for NLCR was 0.73 (confidence interval [CI] 0.66-0.8) compared with 0.62 (CI 0.54-0.70) for CRP. The authors concluded that lymphocytopenia and NLCR are better predictors of bacteraemia than CRP, WCC and NC.

The present study was carried out to evaluate NLCR as a predictor of bacteraemia, compared with WCC,NC, LC and CRP in a large consecutive series of adult patients presenting to the ED with pyrexial illness

**MATERIAL AND METHODS**

Ethical Review:

The study proposal was both internally and externally peer reviewed and ethical approval was granted via the UK's national Integrated Research Application System (IRAS). The Research Committee (institutional review board) of the St Helens and Knowsley Teaching Hospitals NHS Trust approved the study and provided research governance. The consent of participants was deemed unnecessary due to the study design; anonymised data analysis without clinical intervention

Study Design

Retrospective analysis of prospectively collected data.

Setting:

ED of a university-affiliated hospital (annual census 90,000)

Population:

Consecutive adult patients (>17 years) presenting between 1st November 2009 and 31st October 2010 with pyrexial illness. All patients were febrile (tympanic temperature > 37.9<sup>0</sup> C) or met the criteria for sepsis (systemic inflammatory response syndrome due to suspected infection). Patients' records were selected for analysis if they had blood cultures drawn in the ED during the study period. No power calculation was performed

Protocol:

All patients had been managed according to the adult fever protocol of the institution. Paired anaerobic and aerobic blood culture bottles were taken via separate peripheral venepuncture using standardised procedures, and were immediately transported to an on-site laboratory where they were incubated in a Bactec 9240/9120 device (BD Diagnostics Inc, Oxford, UK) at 37 degrees for up to five days.

Haematological parameters were measured on a Sysmex XE-2100 analyser (Sysmex Corporation, Kobe, Japan) while CRP was determined on a fully automated Siemens ADVIA 2400 Chemistry System (Siemens AG, Munich, Germany).

Basic demographic data were recorded, along with the initial blood results for each patient at the time of presentation (WCC, NC, LC and CRP level). The NLCR was then calculated.

Patients with documented haematological malignancy or chemotherapy treatment, and patients on corticosteroid therapy, were excluded. Patients were identified as bacteraemic or non-bacteraemic according to the blood culture results at five days. Microbiology results were reported by a consultant microbiologist. False positive blood cultures, attributed to skin contamination, were excluded from the final analysis.

#### Data Analysis:

Threshold values for each marker were chosen based on previous work by de Jager et al[17]; WCC >  $12 \times 10^9/L$ , NC >  $10 \times 10^9/L$ , LC <  $1 \times 10^9/L$ , CRP > 50 mg/dL and NLCR > 10. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR) and Area Under the Curve (AUC) for each laboratory marker were determined. Non-parametric assumptions were used for the calculation of confidence intervals for AUC. PASS 11 version 11.0.8 and NCSS 2007 (NCSS, LLC, Kaysville, Utah, USA) were used for the analysis of diagnostics test ROC procedures and comparison of AUC respectively.

## RESULTS

2,002 patients (50% male, median age 66 years) met the inclusion criteria. Complete data were available for 1,954. In 48 patients positive blood cultures were attributed to skin contamination. Blood cultures were deemed to be truly positive in 270 patients, giving a prevalence of bacteraemia of 13.8%. Gram negative species predominated among the bacteraemic patients, accounting for 154 isolates (57%), of

which *Escherichia coli* contributed just over half (n=78). *Streptococcus* and *Staphylococcus* species accounted for the gram positive cases in equal measure.

The results of the analyses are presented in Tables 1 and 2. The distribution of WCC was similar in bacteraemic and non-bacteraemic patients (Mann-Whitney U test; p = 0.064). All other variables were significantly differently distributed (p < 0.001).

Receiver Operating Characteristics (ROC) curves (with standard error) for each parameter are presented in figures 1 and 2. NLCR and LC produced the highest AUC at 0.71.

TABLE 1 – Descriptive statistics for diagnostic tests

	Bacteraemia status	Median	Interquartile range	Minimum	Maximum	Mann-Whitney U test	
						Z value	P value
WCC x10 <sup>9</sup> /L	Positive	12.2	8.5 – 18.8	2.0	54.1	-1.63	0.104
	Negative	11.9	8.6 – 15.6	1.6	74.0		
NC x10 <sup>9</sup> /L	Positive	10.9	7.4 – 16.7	1.1	127.0	-3.91	<0.001
	Negative	9.5	6.4 – 13.2	1.0	68.2		
LC x10 <sup>9</sup> /L	Positive	0.7	0.4 – 1.1	0.1	26.3	-10.98	<0.001
	Negative	1.1	0.7 – 1.7	0.1	55.7		
NLCR	Positive	16.0	9.0 – 27.5	0.29	166.0	-11.451	<0.001
	Negative	8.58	4.6 – 14.4	0.22	141.3		
CRP level mg/L	Positive	128.0	47.0 – 245.0	2	522	-8.58	<0.001
	Negative	63.0	19.0 – 146.0	1	539		

WCC – White cell count, NC – neutrophil count, LC – lymphocyte count, NLCR – neutrophil lymphocyte ratio,  
CRP – C-reactive protein  
WCC= White cell count, NC=Neutrophil count, LC=lymphocyte count, NLCR= neutrophil lymphocyte ratio, CRP= C-reactive protein



**TABLE 2 – Performance measures for diagnostic tests**

Variable	Threshold	Sen (95% CI)	Spe (95% CI)	PPV (95% CI)	NPV (95% CI)	LR <sup>-</sup> (95% CI)	LR <sup>+</sup> (95% CI)
WCC	>12	0.51 (0.45, 0.56)	0.51 (0.49, 0.53)	0.14 (0.12, 0.16)	0.87 (0.85, 0.89)	0.97 (0.86, 1.1)	1.03 (0.91, 1.17)
NC	>10	0.54 (0.48, 0.59)	0.53 (0.51, 0.56)	0.15 (0.13, 0.17)	0.88 (0.86, 0.90)	0.87 (0.76, 0.99)	1.15 (1.02, 1.30)
LC	<1	0.68 (0.62, 0.73)	0.61 (0.59, 0.63)	0.21 (0.18, 0.24)	0.92 (0.91, 0.94)	0.53 (0.45, 0.63)	1.73 (1.57 , 1.91)
NLCR	>10	0.70 (0.64, 0.75)	0.57 (0.55, 0.60)	0.20 (0.18, 0.23)	0.92 (0.91, 0.94)	0.53 (0.44, 0.64)	1.63 (1.48, 1.79)
CRP	≥ 50	0.71 (0.66, 0.76)	0.48 (0.46, 0.50)	0.17 (0.15, 0.20)	0.91 (0.90, 0.93)	0.61 (0.50, 0.73)	1.36 (1.25, 1.49)

Sen – sensitivity, spe – specificity, PPV – positive predictive value, NPV – negative predictive value, LR<sup>+</sup> – positive likelihood ratio, LR<sup>-</sup> - negative likelihood ratio, WCC – white cell count, NC – neutrophil count, LC – lymphocyte count, NLCR – neutrophil lymphocyte ratio, CRP – C-reactive protein

Sen=sensitivity, spe=specificity, PPV=positive predictive value, NPV=negative predictive value, LR=likelihood ratio, WCC= White cell count, NC=Neutrophil count, LC=lymphocyte count, NLCR= neutrophil lymphocyte ratio, CRP= C-reactive protein

DISCUSSION

Early diagnosis and initiation of timely broad spectrum antibiotics improves outcome in BSI. Consequently, it is a standard of care to draw blood for cultures before initiation of antibiotic therapy.[18] However, fever and systemic inflammation do not indicate bacteraemia in every case, and there are adverse consequences to the inappropriate prescription of antibiotics; including allergic reactions, *Clostridium difficile* infection and the emergence of antibiotic resistance. At present there is no ideal biomarker for sepsis or bacteraemia, and the gold standard - isolation and identification of bacteria in the blood stream - may be delayed or absent.[19] A suitable marker must provide additional information to that presently available, it must be able to distinguish bacterial infection from other causes of fever, and it should be immediately available and cost effective.[20]

The present study evaluated parameters that are readily accessible as part of the routine work-up of pyrexial adults in the ED. LC and NLCR performed best of these parameters, but offered no advantage over LC alone, in keeping with the findings of Wyllie et al who reported a large study of medically admitted patients. They suggested that the mechanism of the lymphocytopenia was widespread lymphocyte apoptosis induced by the TNF family.[21]

The present findings also echo those of de Jager et al who investigated a small cohort of ED patients.[17] The AUC for both NLCR and LC is similar in both studies (72 vs. 73 and 71 vs. 73 respectively). And both found an AUC for WCC of around 0.5, suggesting that it is a poor indicator of BSI. A notable difference between the two studies is the positive predictive value for NLCR and LC, in the present study 0.20 and 0.21 respectively, compared to 0.70 and 0.68 reported by de Jager. This discrepancy is explained by methodological differences; de Jager et al investigated two groups of matched patients, the consequence of which was that the “prevalence” of bacteraemia was 50%.

Likelihood ratios were generally low for all the variables measured in the present study, indicative of poor diagnostic performance, the post- test probability being little different from pre-test. The diagnostic utility was only marginally better than that of three biomarkers evaluated by Gamaz-Diaz et al in 2011. Among 631 ED patients in that Colombian study sepsis (not BSI) was confirmed in 416 (67%). The authors

concluded that the markers they evaluated, none of them widely available, were not sufficiently sensitive or specific for the diagnosis of sepsis.[22]

In the present study CRP yielded a PPV of 0.71 which was comparable with that of LC and NLCR, but the specificity was significantly poorer than either at 0.48.

### Limitations

The present study was carried out in a single centre and the design was retrospective. Although blood culture-positive and negative groups were similar in terms of age and gender, there may have been other important differences between them. For example, information regarding diagnostic group, co morbidities and discharge status was not available. It was not possible to identify the duration of illness prior to ED presentation, or whether antibiotics had been administered pre-hospital. However, De Jager et al found no difference between bacteraemic and non-bacteraemic cohorts in terms of co-morbidities in their study of 184 patients[17]. And in the present study the relatively large sample size reduces the impact of such confounders.

The *gold standard* in the present study was the detection of viable bacteria in blood culture samples, interpreted at up to five days by a consultant microbiologist. False positive and false negative blood culture results are not uncommon, but are minimised here by a standard protocol for sampling and incubation, on-site laboratory and analysis by an experienced, medically qualified consultant microbiologist who took into account the patterns of positivity, the identity of the organism and the clinical context. The yield of positive blood cultures is similar to that reported in a German study of intensive care patients.[23]

Culture-negative sepsis was not considered in the present study. It is known that a significant minority of patients with severe sepsis and septic shock have no documented evidence of infection, due to prior antibiotic use, inadequate sampling techniques or organisms that are difficult to identify.[24] It is therefore possible that some patients in the present were inappropriately determined to be culture – negative. Nevertheless, the impact on mortality of documented bacteraemia is established and it remains an important endpoint.[1-3]

**CONCLUSIONS**

The present study is the largest to date evaluating NLCR as a predictor of bacteraemia in the ED setting. NLCR is readily available and easy to calculate and at a cut off value of 10 it outperforms conventional markers such as WCC, NC and CRP. NLCR is not a useful diagnostic test in isolation, however, and its significance is similar to that of lymphocytopenia (lymphocyte count < 1.0 ×10<sup>9</sup>/l). None of the parameters investigated proved sufficient in itself to determine which patients must have blood cultures drawn, and those in whom the investigation may be omitted. However, there may be scope for these variables to be incorporated into a clinical scoring system, together with findings in history and examination and other investigations.

**KEY MESSAGES**

- NC and LC are readily available investigations in the management of pyrexial patients in the ED setting, enabling the calculation of NLCR
- LC and NLCR are predictive of blood stream infection
- LC and NLCR outperform traditional diagnostic criteria in suspected infection, including WCC, NC and CRP
- These parameters are insufficient in themselves to determine patient selection for early intravenous antibiotics, but may add diagnostic utility when incorporated into the overall assessment.

**AUTHOR CONTRIBUTIONS**

RL: data collection and analysis, manuscript writing and final approval of the manuscript. CG: data collection and analysis, manuscript writing and final approval of manuscript. IJ: data analysis and presentation, final approval of manuscript. PL: data analysis and presentation, final approval of manuscript. PN: conception and design, manuscript writing and final approval of manuscript. MV: critical revisions of the manuscript and final approval. TE: data collection and analysis, manuscript writing and final approval of manuscript. RS: data collection and analysis, manuscript writing

and final approval of manuscript. HM: data collection and analysis, manuscript writing and final approval of manuscript.

All authors read and approved the final draft. PN conceived the project and takes overall responsibility for the submission

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Competing interests:

The author(s) declare that they have no competing interests

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LEGENDS TO TABLES AND FIGURES

TABLE 1: Descriptive statistics for diagnostic tests

WCC= White cell count, NC=Neutrophil count, LC=lymphocyte count, NLCR= neutrophil lymphocyte ratio, CRP= C-reactive protein

TABLE 2: Performance measures for diagnostic tests

WCC= White cell count, NC=Neutrophil count, LC=lymphocyte count, NLCR= neutrophil lymphocyte ratio, CRP= C-reactive protein

FIGURE1: Receiver Operating Characteristic (ROC) curves

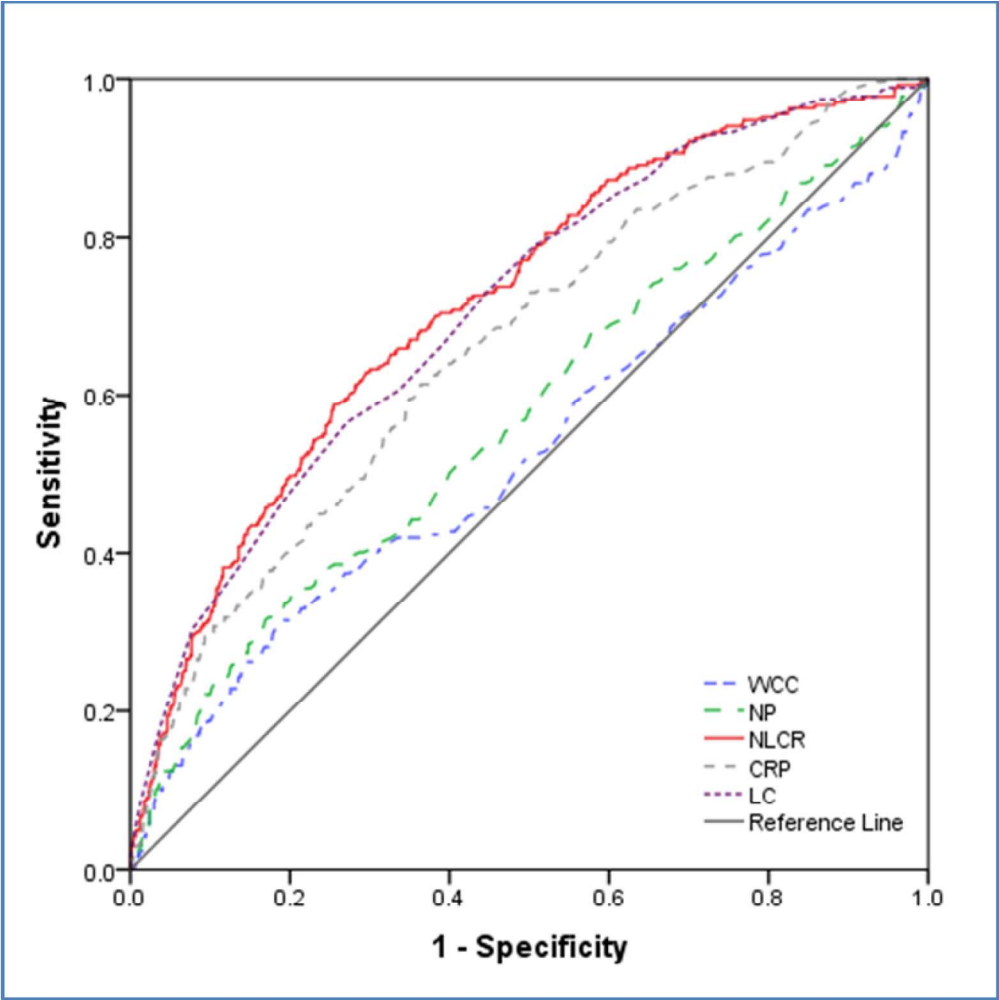
WCC= White cell count, NC=Neutrophil count, LC=lymphocyte count, NLCR= neutrophil lymphocyte ratio, CRP= C-reactive protein

FIGURE 2: Areas under the ROC curves

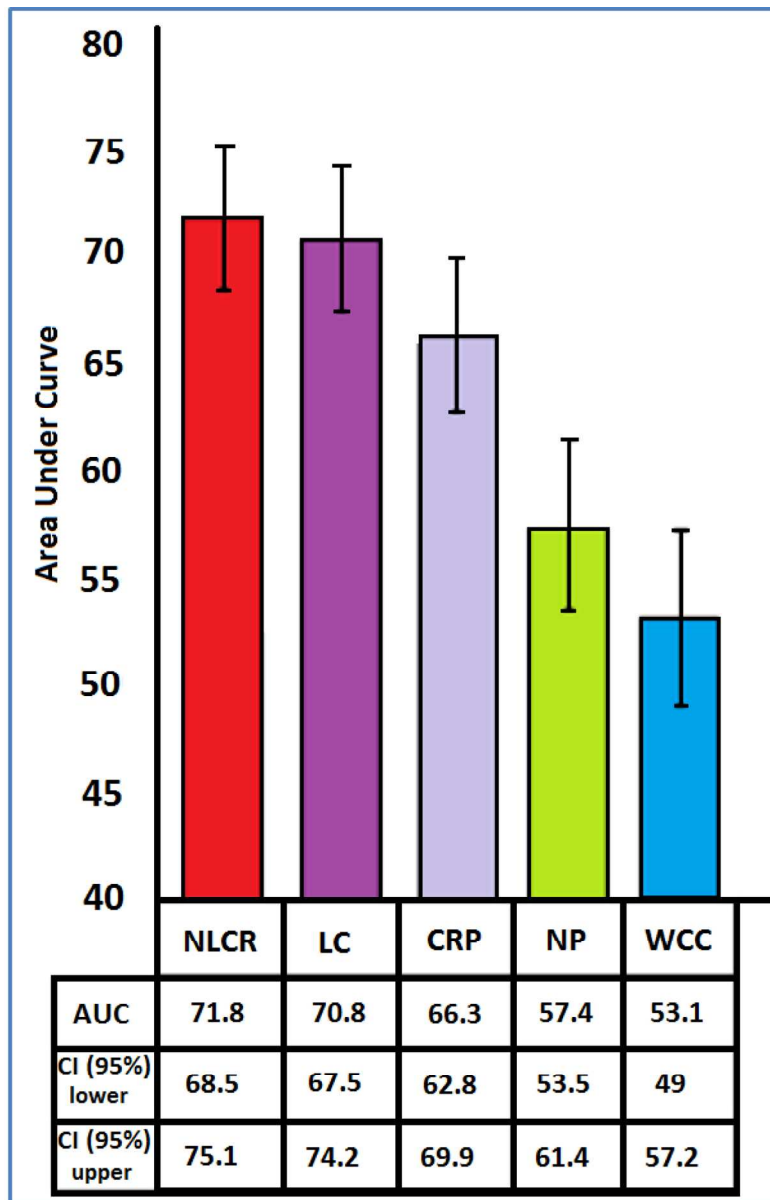
WCC= White cell count, NC=Neutrophil count, LC=lymphocyte count, NLCR= neutrophil lymphocyte ratio, CRP= C-reactive protein



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124x190mm (300 x 300 DPI)