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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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3 **Neutrophil to Lymphocyte Count Ratio as an Early Indicator of Blood Stream**
4 **Infection in the Emergency Department**
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44 **KEY WORDS**
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47 Infection, Bacteraemia, Emergency Department, Neutrophil to Lymphocyte Ratio
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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

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3 Although NLCR outperforms conventional markers of infection it is insufficient in
4 itself to guide clinical management of patients with suspected BSI, and it offers no
5 advantage over lymphocyte count. However, it may offer some diagnostic utility
6 when taken into account as part of the overall assessment.
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9 10 **INTRODUCTION**

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12 The incidence of bacteraemia, defined as the presence of viable bacteria in the
13 bloodstream, in patients admitted to hospital is approximately one per cent. The
14 mortality rate is 25-30%, increasing to 50% when associated with severe sepsis.[1]
15 Patients with blood stream infection (BSI) have worse outcomes than matched
16 culture-negative controls, and early treatment improves the outcome.[2,3] Fever is
17 common in patients presenting to the emergency department (ED), but BSI is
18 confirmed in only a small minority. The presence or absence of infection cannot be
19 confirmed at initial presentation.[4] It would be inappropriate to draw blood for culture
20 in every case and scores have therefore been derived that may improve the yield of
21 positive results. [5]
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25 A variety of physical and biochemical markers are available to the clinician but all
26 have limitations. Clinical features such as the systemic inflammatory response
27 syndrome (SIRS) criteria and the Shapiro score are sensitive indicators of
28 bacteraemia but lack specificity.[5,6,7] Currently available laboratory investigations
29 include the white cell count (WCC) and C-reactive protein (CRP). However, up to
30 50% of patients with bacteraemia may exhibit a normal WCC, and CRP adds little
31 value over and above the neutrophil count (NC) and lymphocyte count (LC).[8,9]
32 Procalcitonin (PCT) has been used to guide antibiotic stewardship in critical care but
33 evidence for its use in the ED setting is limited.[10]
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36 The neutrophil lymphocyte count ratio (NLCR)

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38 The early hyper dynamic phase of infection is characterised by a pro-inflammatory
39 state mediated by neutrophils, macrophages and monocytes with release of
40 inflammatory cytokines such as tumour necrosis factor-alpha (TNF-alpha) and
41 interleukins 1 and 6. This systemic inflammatory response is associated with
42 suppression of neutrophil apoptosis, which augments neutrophil-mediated killing as
43 part of the innate response but may also cause tissue injury.[11] At the same time
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3 lymphocyte apoptosis is increased in the thymus and spleen. This can lead to
4 immune system suppression, multi-organ dysfunction and death.[12]
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7 NLCR is a measure of systemic inflammation [13] and it has been used as a guide to
8 prognosis in community acquired pneumonia[14], ischaemic heart disease[15] and
9 cancer.[16]
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12 NLCR is easily calculated and is immediately available from the full blood count as
13 part of a panel of investigations routinely ordered in admitted patients. Its use in the
14 ED setting could afford the earliest opportunity to identify patients at risk of BSI and
15 the timely administration of antimicrobials.
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20 De Jager et al evaluated the performance of NLCR and other markers of infection in
21 predicting bacteraemia in adults presenting to a Dutch ED.[17] A cohort of 92
22 patients with suspected community acquired bacteraemia and subsequent positive
23 blood cultures were compared with 92 age and sex matched controls with negative
24 blood cultures. There was no significant difference in WCC and NC between the two
25 groups. However, the infected group had significantly lower LC and significantly
26 higher CRP and NLCR. The area under the ROC curve for NLCR was 0.73
27 (confidence interval [CI] 0.66-0.8) compared with 0.62 (CI 0.54-0.70) for CRP. The
28 authors concluded that lymphocytopenia and NLCR are better predictors of
29 bacteraemia than CRP, WCC and NC.
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38 The present study was carried out to evaluate NLCR as a predictor of bacteraemia,
39 compared with WCC,NC, LC and CRP in a large consecutive series of adult patients
40 presenting to the ED with pyrexial illness
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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 > 37.9⁰ 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.

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3 Haematological parameters were measured on a Sysmex XE-2100 analyser
4 (Sysmex Corporation, Kobe, Japan) while CRP was determined on a fully automated
5 Siemens ADVIA 2400 Chemistry System (Siemens AG, Munich, Germany).
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9 Basic demographic data were recorded, along with the initial blood results for each
10 patient at the time of presentation (WCC, NC, LC and CRP level). The NLCR was
11 then calculated.
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14 Patients with documented haematological malignancy or chemotherapy treatment,
15 and patients on corticosteroid therapy, were excluded. Patients were identified as
16 bacteraemic or non-bacteraemic according to the blood culture results at five days.
17 Microbiology results were reported by a consultant microbiologist. False positive
18 blood cultures, attributed to skin contamination, were excluded from the final analysis
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24 25 26 Data Analysis: 27

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29 Threshold values for each marker were chosen based on previous work by de Jager
30 et al[17]; WCC > 12 x10⁹/L, NC > 10 x10⁹/L, LC < 1 x10⁹/L, CRP > 50 mg/dL and
31 NLCR >10. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc.,
32 Chicago, Illinois, USA). The sensitivity, specificity, positive predictive value (PPV),
33 negative predictive value (NPV), likelihood ratio (LR) and Area Under the Curve
34 (AUC) for each laboratory marker were determined. Non-parametric assumptions
35 were used for the calculation of confidence intervals for AUC. PASS 11 version
36 11.0.8 and NCSS 2007 (NCSS, LLC, Kaysville, Utah, USA) were used for the
37 analysis of diagnostics test ROC procedures and comparison of AUC respectively.
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46 **RESULTS**

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48 2,002 patients (50% male, median age 66 years) met the inclusion criteria. Complete
49 data were available for 1,954. In 48 patients positive blood cultures were attributed
50 to skin contamination. Blood cultures were deemed to be truly positive in 270
51 patients, giving a prevalence of bacteraemia of 13.8%. Gram negative species
52 predominated among the bacteraemic patients, accounting for 154 isolates (57%), of
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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 ⁹ /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 ⁹ /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 ⁹ /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 ⁻ (95% CI)	LR ⁺ (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⁺ – positive likelihood ratio, LR⁻ - 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

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3 concluded that the markers they evaluated, none of them widely available, were not
4 sufficiently sensitive or specific for the diagnosis of sepsis.[22]
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7 In the present study CRP yielded a PPV of 0.71 which was comparable with that of
8 LC and NLCR, but the specificity was significantly poorer than either at 0.48.
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11 Limitations

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14 The present study was carried out in a single centre and the design was
15 retrospective. Although blood culture-positive and negative groups were similar in
16 terms of age and gender, there may have been other important differences between
17 them. For example, information regarding diagnostic group, co morbidities and
18 discharge status was not available. It was not possible to identify the duration of
19 illness prior to ED presentation, or whether antibiotics had been administered pre-
20 hospital. However, De Jager et al found no difference between bacteraemic and
21 non-bacteraemic cohorts in terms of co-morbidities in their study of 184 patients[17].
22 And in the present study the relatively large sample size reduces the impact of such
23 confounders.
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33 The *gold standard* in the present study was the detection of viable bacteria in blood
34 culture samples, interpreted at up to five days by a consultant microbiologist. False
35 positive and false negative blood culture results are not uncommon, but are
36 minimised here by a standard protocol for sampling and incubation, on-site
37 laboratory and analysis by an experienced, medically qualified consultant
38 microbiologist who took into account the patterns of positivity, the identity of the
39 organism and the clinical context. The yield of positive blood cultures is similar to
40 that reported in a German study of intensive care patients.[23]
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48 Culture-negative sepsis was not considered in the present study. It is known that a
49 significant minority of patients with severe sepsis and septic shock have no
50 documented evidence of infection, due to prior antibiotic use, inadequate sampling
51 techniques or organisms that are difficult to identify.[24] It is therefore possible that
52 some patients in the present were inappropriately determined to be culture –
53 negative. Nevertheless, the impact on mortality of documented bacteraemia is
54 established and it remains an important endpoint.[1-3]
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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 $< 1.0 \times 10^9/l$). 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

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3 and final approval of manuscript.HM: data collection and analysis, manuscript writing
4 and final approval of manuscript.
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7 All authors read and approved the final draft. PN conceived the project and takes
8 overall responsibility for the submission
9

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13 Financial support:

14 None
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18 Competing interests:

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20 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

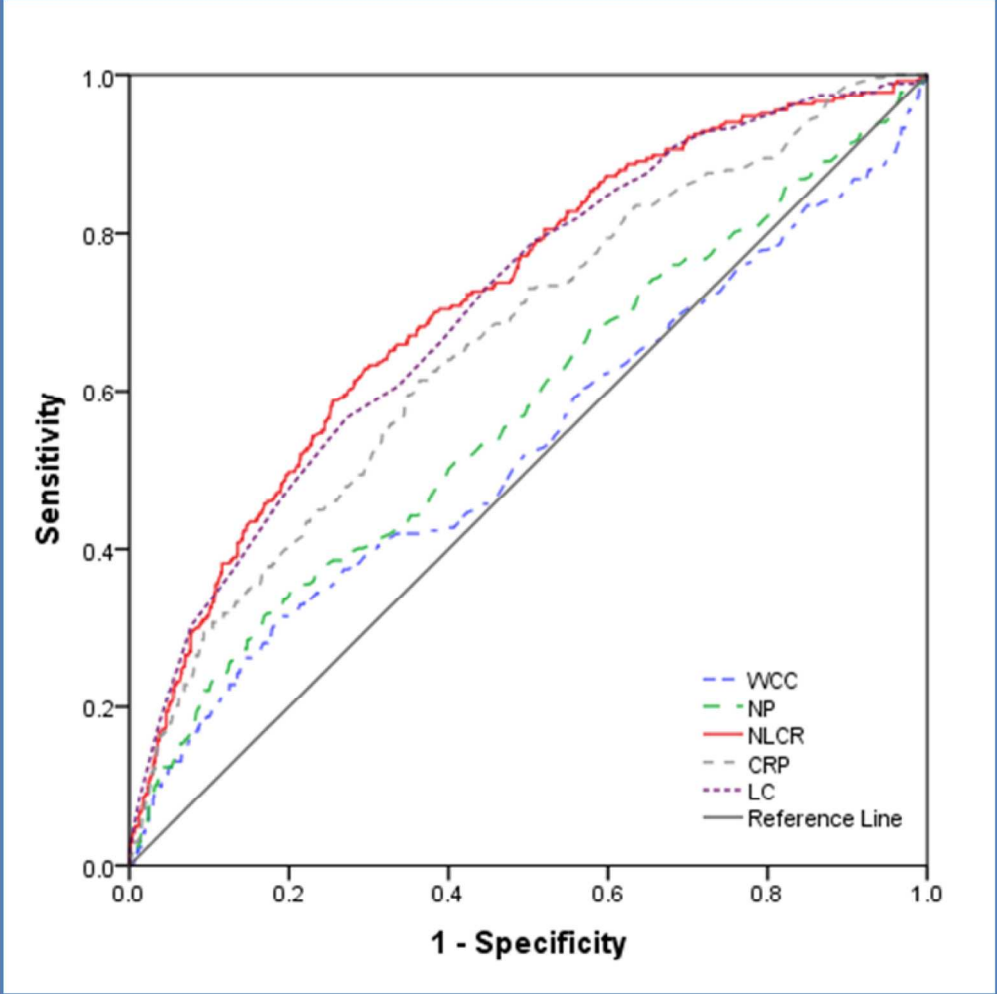
FIGURE 2: Areas under the ROC curves

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

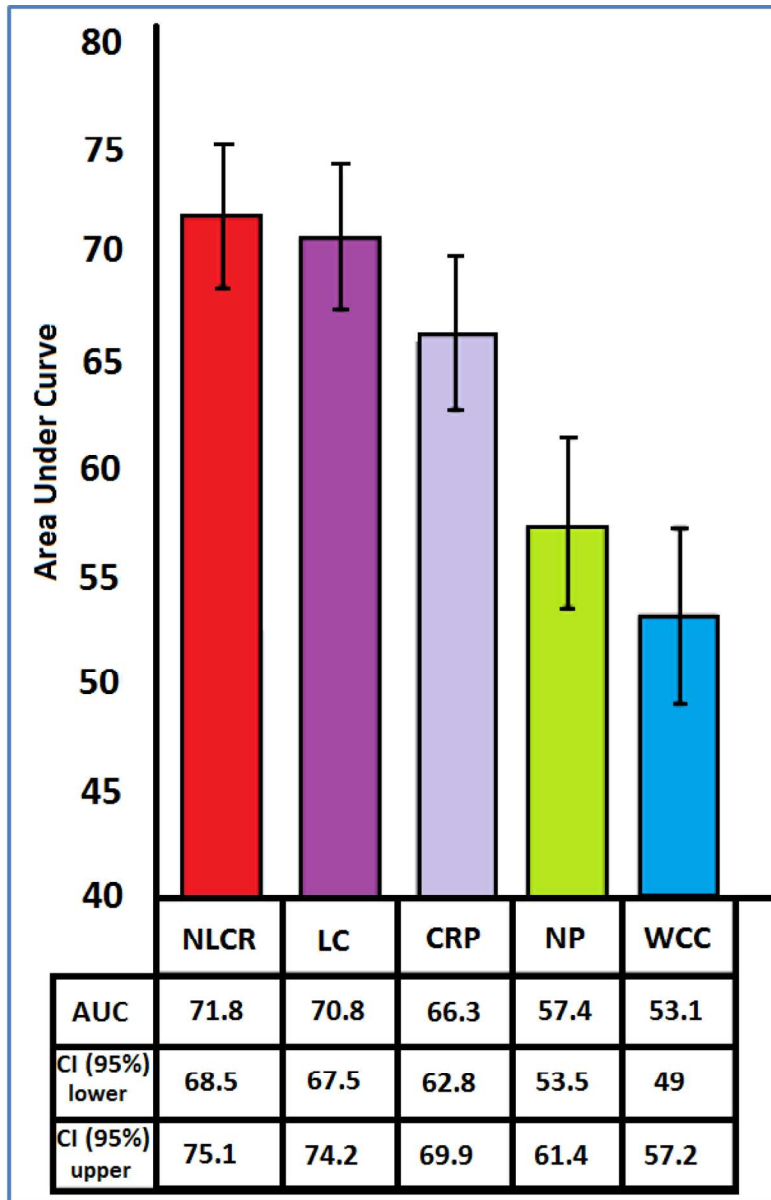
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190x190mm (300 x 300 DPI)



124x190mm (300 x 300 DPI)

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