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Study Of Neutrophil Lymphocyte Count Ratio (NLCR) As A Prognostic Indicator In Patients With Community Acquired Pneumonia.

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ABSTRACT

To determine the utility of Neutrophil Lymphocyte Count Ratio (NLCR) as a prognostic indicator in patients with Community acquired pneumonia (CAP), as well as the role of serum Procalcitonin (PCT) for the same and to compare the effectiveness of NLCR and serum PCT in predicting admission as effective as CURB 65 (confusion, uremia, respiratory rate, BP, age ≥ 65 years). This study was a prospective observational study performed on 207 patients diagnosed with CAP and admitted to the Emergency Department (ED) of a tertiary care hospital. The demographic characteristics, physical examination findings, laboratory results, hospitalizations, and CURB-65 scores of the patients included in the study were recorded on a patient proforma and statistical analyses of this data were conducted. CURB 65 was found to be an effective tool to assess the requirement of hospital admission as well as Intensive Care Unit (ICU). As the risk for hospitalization increased as per CURB 65; the Total Leucocyte Count (TLC), Absolute Neutrophil Count (ANC), NLCR and PCT values increased while Absolute Lymphocyte Count (ALC) values reduced. All the above associations except for PCT were found to be statistically significant with p value <0.05. NLCR and PCT also showed statistical significance with the outcome of death hence proved to be an effective tool to predict the mortality in CAP while there was no significant association of age, gender and Covid status with the outcome in our study. CURB 65, NLCR and Procalcitonin are relatively cost-effective and readily available routine investigations obtained as a part of routine laboratory studies. These indices show good prognostic significance in Community acquired pneumonia.

Keywords: Procalcitonin, Community Acquired Infection, Anionic Neutrophil Activating Peptide, Anionic Neutrophil Activating Peptide

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INTRODUCTION

Community acquired pneumonia (CAP) defined as lung infection contracted by a person outside the healthcare system is one of the most prevalent illnesses that necessitates hospital admissions and is considered as the leading cause of morbidity and mortality worldwide. It is estimated that lower respiratory tract infections constitute around 20% of the mortality due to infectious diseases in India and is responsible for more than 50 billion deaths every year globally [2]. There are no uniform characteristics, and the disease burden varies between geographic locations and is influenced by a number of variables, such as age and host factors [3]. Major risk factors include old age, chronic comorbidities like COPD, impaired airway protection, environmental factors like living in crowded areas like slums, habits like alcohol overuse and smoking, treatments like high dose inhaled corticosteroids, toxins like solvents, paints, gasoline etc [4].

Assessing the requirement for hospitalisation versus outpatient treatment is crucial in the management of CAP, as early hospitalisation and treatment can prevent the development of complications and possible mortality. Many entities based on clinical and laboratory criteria have been developed to assist physicians in making admission decisions such as the CURB - 65 score, Pneumonia Severity Index (PSI), Neutrophil Lymphocyte Count Ratio (NLCR), and Procalcitonin (PCT) [5-8]. Among these CURB -65 criteria is the most recommended for the initial assessment and risk stratification [9]. NLCR is a simple and easy to use tool that can significantly predict the requirement of ICU, respiratory support and mortality among patients admitted with CA [5]. It is based on the role of White Blood Cells in systemic inflammatory response to infection. It is found that following endotoxemia the number of circulating neutrophils increase while lymphocyte count decreases [10].

In this study, both the utility of NLCR as a prognostic indicator in patients with CAP and the role of serum PCT were evaluated. In addition, the efficacy of NLCR and serum PCT in predicting admission relative to CURB 65 was assessed.

MATERIALS AND METHODS

Study Design and setting

This was a prospective observational study done at a tertiary level hospital. The study population comprised of all the patients diagnosed with CAP satisfying the inclusion criteria.

Inclusion Criteria: All adult patients above the age of 18 years, diagnosed as CAP requiring admission to hospital were included in the study.

Exclusion Criteria: Pregnant women and cases of Hospital Acquired Pneumonia (HAP) were excluded from the study.

The diagnosis of CAP was made as per Joint ICS and NCCP guidelines. Chest Radiographs were reviewed by a Radiologist unaware of clinical and laboratory findings. Prior the commencement of the study approval from the institutional ethical committee and written informed consent from admitted patients was obtained.

Data collection and method of measurement

Each patient's complete medical history, comprehensive clinical examination, and pertinent investigations were documented in "Patient Performa" in accordance with a predetermined format. The treatment and final disposal for the patient were also recorded.

All CAP with CURB > 2 were admitted, and within an hour of admission, empirical broad-spectrum antibiotics were initiated. When indicated, sepsis management regimens were also used. Once the culture and sensitivity results were received, antibiotics were changed as necessary. Depending on the clinical characteristics, the treatment lasted between 7 and 10 days. Patients with CURB 0–2 were monitored on an outpatient basis. All patients had their blood NLCR and PCT levels checked at the time of admission, and a computed CURB -65 score was recorded simultaneously for all instances.

Patients' outcomes were examined as either total recovery or death. Documentation was made comparing the results of the CAP with the NLCR and serum PCT. It was documented to compare the therapy results to the CURB-65 score at admission.

Severity of Illness and Outcome

The validated CURB-65 score was computed for each patient upon admission in order to study the severity of CAP at the time of admission. The CURB-65 score is used to estimate the likelihood of mortality in CAP patients [28]. Patients were divided into five risk groups based on this severity score in order to predict mortality.

Statistical Analysis

Data were analyzed via SPSS 21.0 (SPSS Inc., Chicago, IL, USA) software. Results were expressed as number, percentage, mean, median, minimum-maximum values, and standard deviation.

Receiver operating characteristic (ROC) curves was built to assess and compare the sensitivity and specificity of the NLCR, PCT, ALC, ANC and Curb 65 score in predicting mortality. The area under the ROC curves (AUROCs) varied from 0.5 to 1.0 were accepted, with higher values indicating increased discriminatory ability. Confidence intervals of AUCs were calculated with non-parametric assumptions. Each biomarker's discriminant ability was compared according to its individual AUC. For all the comparison in this study, $P < 0.05$ was considered the difference to be statistically significant.

RESULTS

The study involved 207 patients diagnosed with CAP and requiring hospital admission. Mean age of the study participants was 59.10 years with SD of 16.19 years ranging from 21-91 years. Hypertension (38.2%) and Diabetes (43%) were the most common co morbidities observed. Among the patients, 44.9% were Covid positive, 34.3% required ICU admissions while 29 % were under ventilator support. Almost 153 (73.9%) study participants recovered from community acquired pneumonia while 54 (26.1%) of them died.

Severity of CAP and Infection Markers

Table 1 show the frequency and percentage of participants based on their Curb 65 score. 26 (12.6%) and 54 (26.1%) of the study participants, respectively, had CURB 65 scores of 0 and 1, which indicate low risk of hospitalisation. A score of 2 or 3 suggested intermediate risk of hospitalisation in 66 (31.9%) and 54 (26.1%), respectively, whereas a score of 4 indicated high risk of hospitalisation in 7 (3.4%) of the study participants (Figure 1).

Figure 1: Stratification of patients based on their CURB 65 score.

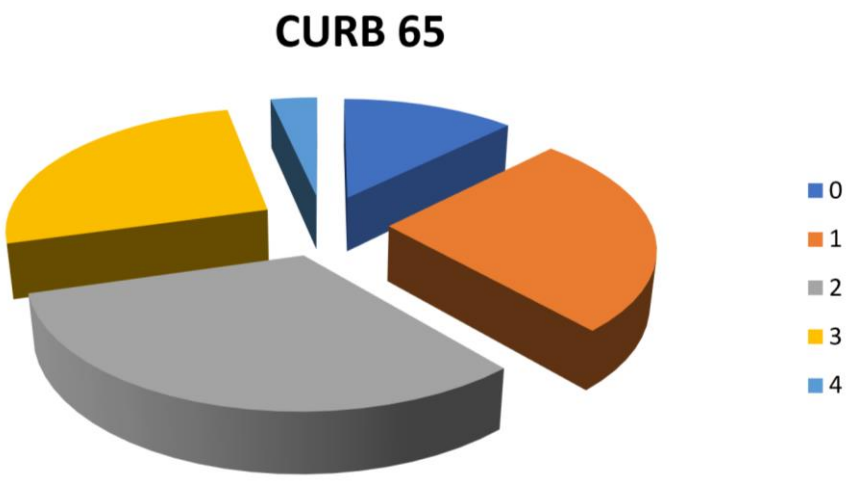

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Table 1: Stratification of patients based on their CURB 65 score.

Risk	CURB 65	Frequency	Percent
Low	0.00	26	12.6
	1.00	54	26.1
Intermediate	2.00	66	31.9
	3.00	54	26.1
High	4.00	7	3.4
	TOTAL	**207**	**100**

During the study period the mean ± SD valves of TLC, Neutrophil, Lymphocyte, ANC, ALC, NLCR, PCT with respect to high values Curb 65 were 11733.29 ± 6789.44, 72.11±13.06, 18.35±10.34, 9012.30 ±6442.45, 1732.33 ±808.07, 6.43±6.61, 2.07±5.01respectively (Table 2) .

Table 2: Descriptive data of continuous study variables.

Parameter	Minimum	Maximum	Mean	SD
TLC (per cu mm)	2400	36000	11733.29	6789.44
Neutrophil (%)	39	98	72.11	13.06
Lymphocyte (%)	2	50	18.35	10.34
ANC (per cu mm)	1320.0	33120.0	9012.30	6442.45
ALC (per cu mm)	476.0	3927.0	1732.33	808.07
NLCR	0.85	49.0	6.43	6.61
Procalcitonin (ng/ml)	0.001	65.0	2.07	5.01
Blood Urea Nitrogen (mg/dl)	10	259	34.43	25.48
Systolic Blood Pressure (mm Hg)	72	200	127.50	19.57
Diastolic Blood Pressure (mm Hg)	48	110	76.14	11.85
CURB-65	0	4	1.83	1.06

As the CURB-65 score increased from score 0 to 4 , the TLC, ANC, NLCR and PCT values increased consistently while ALC values reduced. All the above associations except for PCT were found to be statistically significant with p value <0.05 (Table 3).

Table 3: Association of CURB 65 scores with haematological parameters.

CURB 65	Low risk	Intermediate risk	ICU admission	P value
	0-1	**2-3**	**3-4**	
TLC	8813.75 (4105.19)	13450.75 (7415.70)	15657.14 (8914.19)	<0.0001
ANC	6093.46 (3820.25)	10682.18 (6964.18)	13744.00 (8686.38)	<0.0001
ALC	1870.03 (884.22)	1671.93 (741.61)	1194.00 (743.48)	0.047
NLCR	4.421 (5.90)	7.33 (6.31)	14.13 (10.48)	<0.0001
PCT	1.40 (2.71)	2.36 (6.13)	4.73 (1.78)	0.150

According to area under ROC curves analysis, the AUCs of Curb65, ANC, ALC, NLCR and PCT were 0.646,0.504,0.434,0.515 and 0.632 (95% CI, p <0.05) respectively. Higher value of AUC indicated higher discriminatory ability. The cut off value of each biomarker was calculated and sensitivity and specificity were recorded (Table 4). NLCR and PCT had higher sensitivity and specificity with p value less than 0.05. As per the survival analysis, all of the biomarkers chosen for this study exhibited good potential for predicting the outcomes of critically ill patients (Table 5)

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Table 4: The Area Under of the ROC Curves in the Factors Predicting CAP-Related In-Hospital Mortality.

	AUC	95 % CI	Cut off	Sensitivity (%)	Specificity (%)	p
Curb 65	0.646	0.56-0.73	2.5	50	77.3	<0.0001
ANC	0.504	0.408-0.60	9205	51.9	60.1	< 0.05
ALC	0.434	0.338-0.529	1020	70.4	20.3	< 0.05
NLCR	0.515	0.429-0.601	2.63	81.5	27.5	< 0.05
PCT	0.632	0.54-0.72	1.89	53.7	72.5	<0.05

Table 5: Association of Biomarkers with the outcome of the patient.

		Outcome		p value
		Recovered	Died	
CURB 65	<2.5	119 (81.5%)	27 (18.5%)	<0.00001
	≥2.5	34 (55.7%)	27 (44.3%)	
ANC	<9205	94 (79.7%)	24 (20.3%)	<0.05
	≥9205	59 (66.3%)	30 (33.7%)	
ALC	<1020	29 (61.7%)	18 (38.3%)	<0.05
	≥1020	124 (77.5%)	36 (22.5%)	
NLCR	<2.62	44 (84.6%)	8 (15.4%)	<0.05
	≥2.62	109 (70.3%)	46 (29.7%)	
PCT	<1.89	111 (81.6%)	25 (18.4%)	<0.05
	≥1.89	42 (59.2%)	29 (40.8%)	

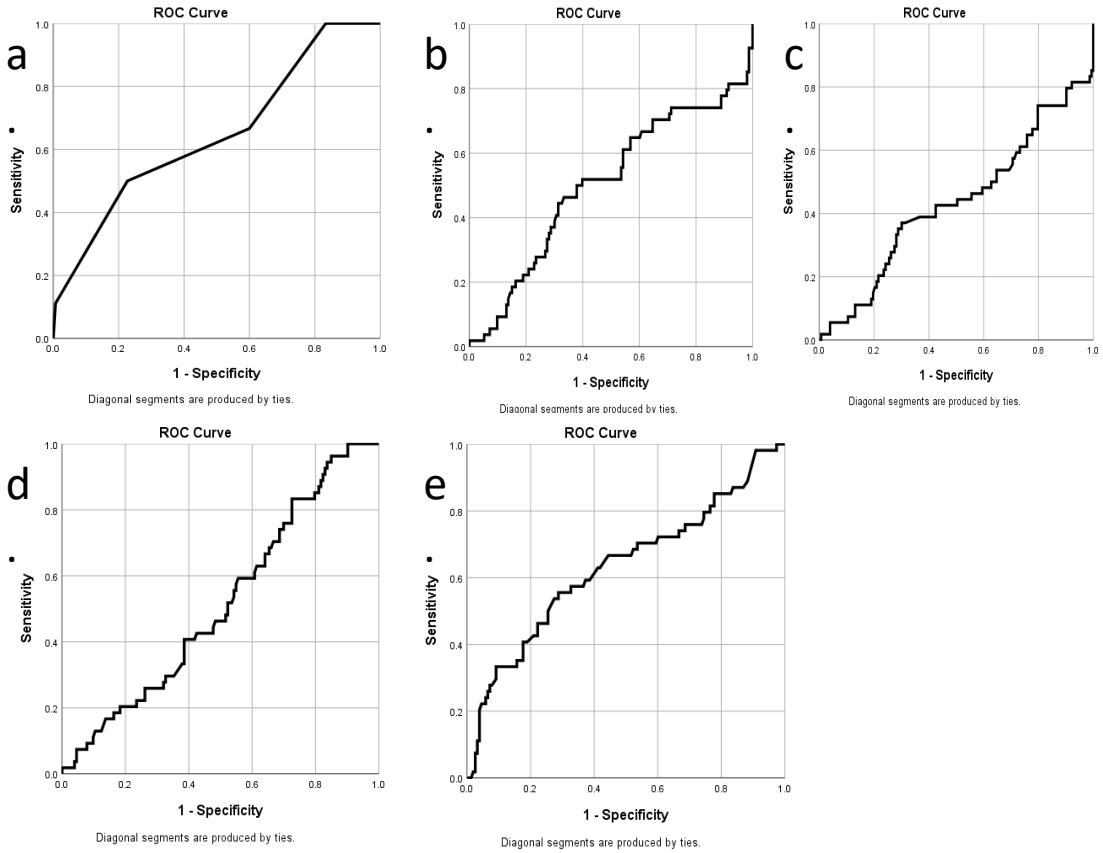

Figure 2: ROC curve for a. Curb 65, b. Absolute Neutrophil Count (ANC), c. Absolute Lymphocyte count (ALC), d. Neutrophil lymphocyte count ratio(NLCR), e. Procalcitonin

DISCUSSION

CAP raises the hospital admissions and medical expenses globally and often leads to morbidity and mortality hence their early prediction is critical. Diagnostic markers like PCT, NLCR and changes in WBC populations have been recently included in clinical practice [11]. PCT is fast and specific marker for infection but their high cost serve as their major limitation while NLCR is cost effective and doesn't require any special instrument for measurements. The quick kinetics of the changes in WBC populations reflects the role of neutrophils in the initial stages of the inflammatory response. It has also been proposed that lymphocytopenia, which frequently coexists with neutrophilia, is a reliable indicator of bacteremia [12]. In the present study we studied the effectiveness of NLCR and PCT as prognostic factors for CAP. The results indicate that the NCLR, PCT and Curb 65 were all discriminant between survival and mortality group.

Present study showed that mean (SD) age of the patients who recovered was 58.71 (17.76) compared to 60.22 (10.61) among non survivors and the association was not statistically significant compared to other similar studies which showed a higher mean age. There was no significant association of comorbidities like diabetes with the outcome of the patient.

Curb 65 has been used widely since inception and has been extensively validated. Capelastegui A et al conducted one of the largest studies on 1776 patients including 1100 in patients and 676 outpatients [13]. The 30 days mortality rate increased in direct proportion to the increasing CURB 65 score. The rate was 0% for CURB 65 score of 0 and increased to 60% for a CURB 65 score of 5. They also noticed that the higher the score, higher is the need for mechanical ventilators and hospital admission and with duration of hospital stay among inpatients(65) The observed increase in the hospitalisation with Curb 65 score in our study was expected. When a cut off 2.5 was taken for CURB 65 according to the ROC curve, 18.5% of those with CURB65 score less than 2.5 died compared to 27 (44.3%) of them with a CURB65 score of more than 2.5 which was statistically significant with p value <0.0001 hence was found to be an effective tool to assess the requirement of hospital admission as well as ICU. As the risk for hospitalization increased as per CURB 65; the TLC, ANC, NLCR and PCT values increased while ALC values reduced. All the above associations except for PCT were found to be statistically significant with p value <0.05.

ROC curve for ANC and ALC had an AUC of 0.504 (95% CI of 0.408-0.60) and 0.434 (95% CI of 0.338-0.529) and a cut off 9205 cells/ml and 1020 cells/ml. The cut off gave a statistically significant association with the outcome. Nirgude D et al showed a mean (SD) ANC of 15848.88 (1256.13) among non survivors and 19962.63 (1946.09) and a mean (SD) ALC of 1455.92 (449.29) in those who did not survive compared to 1207.05 (210.99) in those who survived but this association was not significant [14].

Numerous studies have shown that NLCR, a relatively novel biomarker, can predict the outcomes of different oncology patients and can be used as a prognostic factor before surgery in patients with colorectal cancer [15–18]. NLCR is an effective tool to predict the mortality in CAP. In our study, higher NLCR ratios were associated with mortality. The present study showed that a mean NLCR of 4.42 (5.9) in those treated as out-patient, 7.33(6.3) in those who needed hospital admission and 14.3 (10.48) in those who were admitted in the ICU. Hence it can be used as stratification tool on the lines of CURB -65. It will require further validation. Similarly higher NLCR was associated with mortality. NLCR > 2.63 had shown a sensitivity of 81.5% and specificity of 27.5% and gave a significant association with the outcome of death with p value of 0.04. Similar study done by Yang T et al showed that a cut off 7.12 gave a sensitivity of 82.61% and specificity of 64.75%. The cut off in this study was high compared to that in our study with similar sensitivity but had higher specificity than our study. Procalcitonin has also shown statistically significant association with the outcome of death. An area under the curve of 0.632 was seen with the ROC curve for Procalcitonin with 95% CI of 0.54-0.72 and a cut off 1.89ng/ml had a sensitivity of 53.7% and specificity of 72.5% which had a statistically significant association with the outcome.

The AUC of the NLCR ROC curve was higher than that of conventional markers, especially ALC, ANC while comparable to Curb 65 and PCT in predicting mortality in CAP patients. This finding is in accordance with a previous study [15-20] documenting the importance of the NLCR in the prediction of CAP.

Limitation

This study has various limitations as the microbiological diagnosis was not studied. The complete sample size was not taken in view of prevailing COVID 19 pandemic. Also The effect of prior antibiotics use and steroids were not taken into consideration.

CONCLUSION

CURB 65, NLCR and Procalcitonin are relatively cost-effective and readily available routine investigations obtained as a part of routine laboratory studies. These indices show good prognostic significance in CAP. Their utility in clinical algorithms can better guide management of patients.

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