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COMPARATIVE STUDY OF NEUTROPHIL-TO-LYMPHOCYTE RATIO TO N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE IN PREDICTING SEVERITY OF HEART FAILURE IN PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

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Abstract

Background: The most common consequence of all cardiac disorders, heart failure is a clinical condition that is the predominant factor in morbidity, death, and hospitalization in this patient population. Present study was aimed to compare neutrophil-to-lymphocyte ratio (NLR) to N-terminal pro-b-type natriuretic peptide (NTproBNP) in predicting severity of heart failure in patients with acute decompensated heart failure. **Material and Methods:** Present study was single-center, prospective, observational study, conducted in patients of age > 18 years, either gender, admitted with symptoms and signs of acute decompensated heart failure. The NLR was computed as the ratio of neutrophil to lymphocyte percentage. In addition, samples for NT-pro BNP were collected at the time of admission from research participants. **Results:** During the course of treatment, 12 patients (15 %) expired in the hospital. Total of 12 patients were died during the course of treatment. Among that 8 patients had an admission NLR of more than 7.75. Only 4 patients with NLR less than 7.75 were died in the hospital. NLR > 7.75 was significantly associated with mortality. Among 12 patients who died, 10 patients had an admission NT-PRO-BNP of more than 5635. NT-PRO-BNP > 5635 was significantly associated with mortality ($p<0.001$). In present study, higher levels of NLR, NT-PRO-BNP were significantly associated with ICU admission &

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prolonged hospital stay. In present study, higher levels of NLR, NT-PRO-BNP were significantly associated with reduced EF thus severity of heart failure. **Conclusion:** In patients with acute decompensated HF, NLR is a clinically useful, cost-effective value that forecasts in-hospital mortality, length of hospital stay & severity of heart failure.
Keywords: heart failure, NLR, NTproBNP, decompensated failure

Introduction

The most common consequence of all cardiac disorders, heart failure is a clinical condition that is the predominant factor in morbidity, death, and hospitalization in this patient population. Heart failure (HF) and cardiac dysfunction, which are currently major health issues, affect about 26 million individuals worldwide.[1,2] With the ageing population, the worldwide burden of heart failure and cardiac dysfunction is rising quickly and significantly. The identification of heart failure and cardiac dysfunction is crucial in clinical practice because of the high morbidity and mortality rates.

Both HF with reduced ejection fraction and HF with intact ejection fraction are susceptible to myocardial injury, detrimental left ventricular remodeling, and disease progression brought on by neutrophil- and T-cell-derived enzymes and cytokines. A developing biomarker for assessing the risk and prognosis of cardiovascular disorders is the neutrophil-to-lymphocyte ratio (NLR).[3,4]

Brain Natriuretic peptide (BNP) is primarily secreted by the heart and released into the bloodstream in response to increased heart wall stretching brought on by increased volume and pressure overload.[5] Currently, the most potent predictive biomarkers for heart failure are BNP measurement and its physiologically inactive N-terminal fragment (NTproBNP).[6] Present study was aimed to compare neutrophil-to-lymphocyte ratio (NLR) to N-terminal pro-b-type natriuretic peptide (NTproBNP) in predicting severity of heart failure in patients with acute decompensated heart failure.

Material And Methods

Present study was single-center, prospective, observational study, conducted in department of general medicine, at Government Royapettah Hospital, Chennai-14, India. Study duration was of 6 months (May 2022 to October 2022). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients of age > 18 years, either gender, admitted with symptoms and signs of acute decompensated heart failure, willing to participate in present study

Exclusion criteria

- Patients with medical conditions known to affect the total and differential WBC counts, such as History of hemorrhagic disease, Clinical evidence of active infection, Malignancies, Recent corticosteroid use within 3 months prior to admission, Systemic autoimmune diseases, End stage renal disease, End stage liver disease, Sudden death in casualty
- Conditions associated with elevated NT pro-BNP values such as Acute coronary syndrome, Myocarditis, Valvular heart disease, Hypertrophic cardiomyopathy,

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Cardiotoxic drugs, Atrial fibrillation or flutter, Right ventricular dysfunction in the setting of significant pulmonary disease (pulmonary hypertension, pulmonary embolism), Stroke, High output states

Sample size was determined based on the study by Durmus E *et al.*, & the sample size calculated to be 72.[7] Study was explained to patients in local language & written consent was taken for participation & study. All patients underwent thorough history taking & a thorough clinical examination, findings were recorded into the proforma. Basic traits such as diabetes, hypertension, coronary artery disease, dyslipidemia, chronic renal disease, and a history of addictions such as smoking and drunkenness were taken into account. During the physical examination, signs of decompensation such as tachycardia, tachypnea, elevated JVP, pedal edema, and cold periphery were sought after.

At the time of admission, total WBCs, neutrophils, and lymphocytes were counted along with automated differential counts, and data was entered. The NLR was computed as the ratio of neutrophil to lymphocyte percentage. In addition, samples for NT-pro BNP were collected at the time of admission from research participants. Other baseline investigations like ESR, RBS, RFT & LFT were done in all patients.

ECG and chest X-ray results from the day of admission were also recorded. The primary purposes of the ECG were to evaluate heart rhythm and identify LV hypertrophy or a history of MI (presence or absence of Q waves). In chest radiography, looked for findings of pulmonary edema, pulmonary venous congestion, pulmonary vascular redistribution–cephalization, cardiomegaly, pleural effusions, Kerley lines, etc. All study participants underwent echocardiography, to evaluate valvular, wall motion, chamber size, hypertrophy of part or all of the myocardium, and left ventricular ejection fraction. All patients enrolled into the study were followed up till discharge or death during hospital stay

The SPSS version 21.0. was used to analyse all the data that were entered into a Microsoft Excel sheet. Quantitative factors were expressed as mean and standard deviation, whereas qualitative variables were expressed as proportions and percentages. The Pearson Chi-Square test and odds ratio were used to assess the strength of the associations between different parameters.

Results

A total of 80 patients with acute decompensated heart failure were enrolled into the study. The mean age of the study population was 59.8 ± 6.7 years. Majority patients were aged more than 60 years (51.3 %), were males (67.5%), presented with NYHA class 3 symptoms (46.3%). Common comorbidities were hypertension (47.5%), diabetes (55 %), dyslipidemia (50 %), coronary artery disease (50 %) & chronic kidney disease (eGFR > 30ml/min/1.73 m2) (32.5 %). Among study population 35 (43.8%) patients were alcoholic. Smoking was present in 29 (36.3%)patients.

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Table 1- General characteristics

	No. of patients	**Percentage**
Age groups (in years)		
<50	10	12.5%
51-60	29	36.3%
>61	41	51.3%
Mean age (mean ± SD)	59.8 ± 6.7	
Gender		
Female	26	32.5%
Male	54	67.5%
NYHA class		
1	2	2.5%
2	17	21.3%
3	37	46.3%
4	24	30.0%
Comorbidities		
Hypertension	38	47.5%
Diabetes mellitus	44	55.0%
Dyslipidemia	40	50.0%
Coronary artery disease	40	50.0%
Chronic kidney disease	26	32.5%
Addictions		
Alcohol	35	43.8%
Smoking	29	36.3%

Most common finding in the ECG of the patients was sinus tachycardia (56.3%). Normal sinus rhythm was seen in 11 (13.8%) patients.

Table 2- ECG changes

ECG	**Frequency**	**Percent**
Sinus tachycardia	45	56.3%
NSR	11	13.8%
LVH+ST	7	8.8%
PPRW+ST	6	7.5%
LVH	5	6.3%
LBBB	2	2.5%
RBBB + Sinus tachycardia	2	2.5%
PPRW	1	1.3%
RBBB	1	1.3%

Most common finding in chest x-ray was stage II pulmonary edema, (45 %) i.e., interstitial edema which presents as perivascular, peribronchial, interlobular, subpleural effusion and Kerley's lines.

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Table 3 – Chest X-ray findings

Chest X-ray findings (stage of pulmonary edema)	Frequency	Percent
Stage I– upper lobe veins more prominent than lower lobe	21	26.3%
Stage II- interstitial edema	36	45.0%
Stage III–Intra-alveolar edema (bilateral patchy opacities)	23	28.8%
Stage IV- hemosiderosis, ossification	0	0

Only 2 patients were able to tolerate room air. 50 % of the patients required noninvasive ventilation in the form of CPAP. 14 (17.5%) needed mechanical ventilation due to respiratory distress.

Table 4- Oxygen requirement

Oxygen requirement	Frequency	Percent
Room Air	2	2.5%
Oxygen (O_2)	24	30.0%
Non Invasive Ventilation (NIV)	40	50.0%
Mechanical Ventilation (MV)	14	17.5%

During the course of treatment, 12 patients (15 %) expired in the hospital.

Table 5- Mortality

Mortality	Frequency	Percent
No	68	85.0%
Yes	12	15.0%

Total of 12 patients were died during the course of treatment. Among that 8 patients had an admission NLR of more than 7.75. Only 4 patients with NLR less than 7.75 were died in the hospital. NLR > 7.75 was significantly associated with mortality.

Table 6- Relation of NLR & mortality

		MORTALITY		Total
		Yes	No	
NLR	>7.75	8	2	10
	<7.75	4	66	70
Total		12	68	80

NLR	
Cutoff	7.75
AUC	0.782
P value	0.002
Sensitivity	66.67%
Specificity	97.06%
PPV	80.00%
NPV	94.29%

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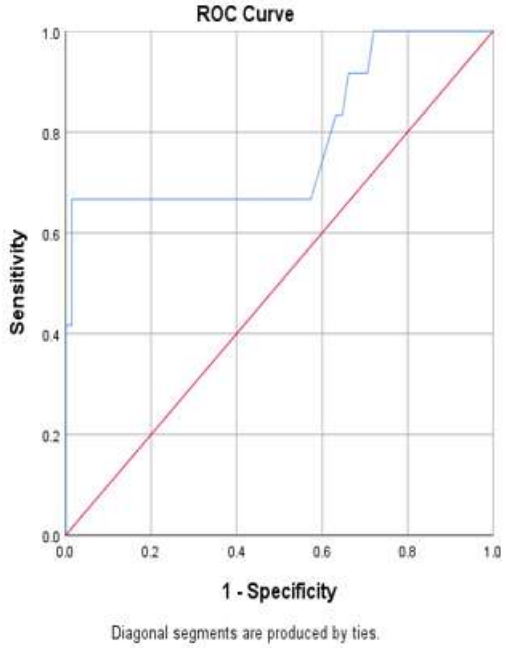
Accuracy	92.50%



Figure

Among 12 patients who died, 10 patients had an admission NT-PRO-BNP of more than 5635. NT-PRO-BNP > 5635 was significantly associated with mortality (p<0.001).

Table 7- Relation of NT-PRO-BNP & MORTALITY

		MORTALITY		
		Yes	**No**	**Total**
NT- PRO-BNP	>5635	10	19	29
	<5635	2	49	51
Total		12	68	80

NT-pro-BNP	
Cutoff	5635
AUC	0.834
P value	<0.0001
Sensitivity	83.33%
Specificity	72.06%
PPV	34.48%
NPV	96.08%
Accuracy	73.75%

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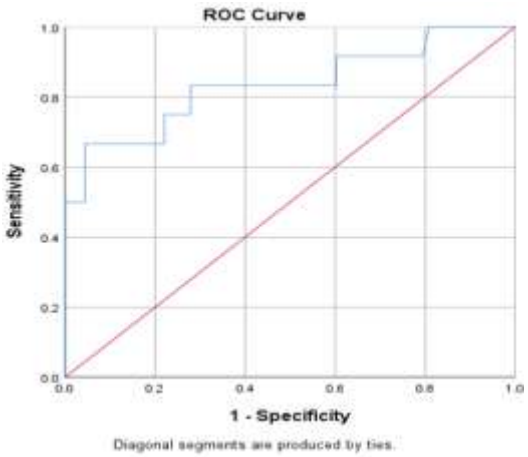

Figure

In present study, higher levels of NLR, NT-PRO-BNP were significantly associated with ICU admission & prolonged hospital stay.

Table 8 – Correlation of NLR, NT-PRO-BNP with ICU admission, duration of hospital stay

		ICU	DURATION
NLR	Pearson Correlation	.670**	.551**
	P value	<0.0001	<0.0001
NT-PRO- BNP	Pearson Correlation	.645**	.590**
	P value	<0.0001	<0.0001

In present study, higher levels of NLR, NT-PRO-BNP were significantly associated with reduced EF thus severity of heart failure.

Table 9 – Correlation of NLR, NT-PRO-BNP with EF

		EF
NLR	Pearson Correlation	-.780**
	P value	<0.0001
NT-PRO- BNP	Pearson Correlation	-.716**
	P value	<0.0001

Discussion

NLR is a composite biomarker that incorporates two distinct immune pathways: Lymphopenia is linked to physiological stress, and neutrophils are involved in active non-specific inflammation.[8] In healthy individuals, NT-proBNP has a steady action as a metabolite of BNP. After the onset of HF, patients frequently develop ventricular remodeling and cardiac insufficiency, which increases atrial pressure, stimulates the release of BNP from the atrial wall's myocardium, and causes BNP to be rapidly synthesized and released into the blood, increasing patient NT-proBNP levels. The research team led by Schmitt discovered that NT-pro BNP has a stronger predictive value for cardiac insufficiency than clinical data from HF studies.[9,10]

High NLR has been linked to a number of cardiovascular diseases, and it has been

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argued that NLR is a reliable indicator of inflammation. It's significant to note that there aren't any globally accepted cutoff values for NLR that categorize health outcomes as normal or poor. Studies frequently choose different NLR cutoff criteria and fail to take into account well-known population differences (such as those between Asian and African populations) in the normal range of neutrophil and lymphocyte counts. Therefore, it may be appropriate to take into account underlying genetic diversity, which can impact estimations of what is considered normal, when using NLR ratios as a predictive marker for health outcomes.

One of the most prevalent leukocyte types, neutrophils are implicated in ongoing, non-specific inflammation. As a result of abnormally high neutrophil activity during inflammation, several proinflammatory factors and proteolytic enzymes are released, amplifying the inflammatory response and destroying cardiomyocytes, thus impairing heart function. Lymphocyte has a connection to physiological stress and is crucial in inflammation. The decrease in lymphocyte level in HF patients is caused by decreased lymphocyte proliferation and differentiation, suppression of neurohumoral priming, and lymphocyte death.[11,12]

The ability of NLR, a composite neutrophil and lymphocyte inflammatory marker, to simultaneously reflect neutrophil and lymphocyte evaluation characteristics, reflect sympathetic nerve excitation, and more accurately reflect the inflammatory state is of great significance for the assessment of the condition and prognosis of patients with HF.[13,14]

In our study, NLR value of more than 7.75 was associated with high in- hospital mortality with a p value of < 0.002. In case of NT-proBNP cutoff value taken was 5635; above this level had a high mortality with p value of <0.0001. On correlating the values of NLR and NT-proBNP in predicting the severity, need for ICU care, duration of ICU stay and in-hospital mortality, the p value obtained was <0.0001.

The ROC analysis in this study also revealed that NLR and NT-pro BNP had respective AUCs of 0.782 and 0.834 in assessing in-hospital mortality. The findings suggest that NLR and NT-proBNP are useful in predicting death. The advantages of NLR detection include easy access, low cost, faster detection, among others, and less detection variability. Lower detection costs and improved prediction results are benefits of NT-pro BNP detection. However, there are still some drawbacks to solely employing NLR or NT-pro BNP to predict the prognosis of HF, including age, infection, renal function, and single-index detection.[15]

Limitations of present study were, unable to determine how these variables changed over time or how these changes affected HF outcomes. It's a single center, observational study; multi-center randomized controlled trials are needed to eliminate bias and find out standard values. No conventional cutoffs are provided for both NLR and NT-pro BNP in predicting mortality and outcomes. Therefore, this study requires additional standardized trials.

Conclusion

In patients with acute decompensated HF, NLR is a clinically useful, cost-effective value that forecasts in-hospital mortality, length of hospital stay & severity of heart failure. Elevated NLR in HF at the time of admission is a reliable indicator of both the length of hospital stays

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and short-term death. From this study the cut-off value of NLR is 7.75 to use it as prognostic marker in HF. We suggest that our study results should be taken in to consideration in treatment for patients with acute decompensated HF.

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