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Association of Inflammatory Burden Index (IBI) with Clinical Outcomes in Acute Exacerbated COPD (Chronic Obstructive Pulmonary Disease) Patients with Respiratory Failure: Hospital based observational study

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ABSTRACT

Background

Acute exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) accelerate disease progression and increase healthcare burden. Systemic inflammation is a key contributor, yet comprehensive inflammatory markers for predicting ventilatory support needs remain underexplored. The Inflammatory Burden Index (IBI), integrating C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR), may serve as a novel prognostic tool for non-invasive ventilation (NIV) dependency

Materials and methods

This observational cross-sectional study was conducted in a tertiary care hospital over six months, enrolling 64 AECOPD patients requiring hospitalization. IBI was calculated using CRP, neutrophil, and lymphocyte counts, and its association with NIV requirement at discharge was assessed. Data were analyzed using Mann-Whitney U test, Spearman's correlation, and receiver operating characteristic (ROC) curve analysis to evaluate the predictive accuracy of IBI compared to other biomarkers.

Results

Patients with elevated IBI levels (79.4 ± 26 vs. 22.6 ± 27.1, $p<0.001$) were more likely to require NIV at discharge. IBI showed a strong positive correlation with pCO_2 ($r=0.696$, $p<0.001$) and a negative correlation with FEV1 ($r=-0.465$, $p<0.001$). ROC analysis demonstrated IBI's superior predictive ability (AUC = 0.89, $p<0.001$) compared to NLR and CRP.

Conclusion

IBI is a strong predictor of NIV dependency and may aid in early risk stratification and treatment planning. Further multi-center validation is warranted to confirm its clinical utility.

Keywords: *Acute Exacerbation, COPD, Inflammatory Burden Index, Non-Invasive Ventilation, Observational Study, Prognostic Biomarker*

HIGHLIGHTS

The Inflammatory Burden Index (IBI), which consolidates measures such as CRP, and Neutrophil-to-Lymphocyte Ratio (NLR), emerges as a promising prognostic tool. Current prognostic approaches largely rely on individual inflammatory markers, which do not fully capture the cumulative burden of systemic inflammation in disease progression

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) ranked as the fourth leading cause of death globally, accounting for 3.5 million deaths and approximately 5% of all worldwide fatalities.[1] The clinical trajectory of COPD is notably worsened by acute exacerbations (AECOPD), which not only hasten the disease's progression but also significantly increase both hospitalization rates and the likelihood of long-term dependence on ventilatory support.[1,2]A hallmark of AECOPD episodes is an intensified inflammatory response, both within the airways and systemically, which correlates with diminished respiratory function and a heightened mortality risk . [3]

India's struggle with COPD is particularly pronounced, with a prevalence rate of 7.4% among those aged 40 and above, and nearly one million deaths attributed to this condition annually. The situation is acute in South India, where exposure to biomass fuels, occupational hazards, and a high prevalence of smoking contribute to the disease's severity. [4,5] Similar patterns of AECOPD leading to hospital admissions, extended ICU stays, and considerable economic burdens through recurrent hospitalizations and ventilation needs are observed across several developing countries. [6-8] Despite advances in treatment, the management of AECOPD remains a challenge due to the limited ability to predict disease progression and identify patients at risk for long-term ventilatory support. There is a pressing need for a more comprehensive and reliable biomarker-based index that can enhance risk stratification and guide early therapeutic decisions.

In the realm of AECOPD management, the role of inflammatory biomarkers has been explored, [9-11] yet there remains a gap in identifying a comprehensive index capable of reliably predicting clinical outcomes. By encompassing the overall inflammatory load, the IBI (Inflammatory Burden Index) provides insights into disease severity and the risk of ventilatory dependence in a more holistic manner than individual biomarkers.

The present study addresses a substantial deficit in existing prognostic models, which frequently fail to account for the aggregate effects of systemic inflammation. Our research endeavors to assess the efficacy of the Inflammatory Burden Index (IBI) in predicting the necessity for NIV at the point of hospital discharge.

Materials and methods

This observational study was conducted in a tertiary care hospital setting; after securing approval from IHEC, also appropriate measures were taken to protect privacy and confidentiality of patient’s information. Consecutive sampling was employed to enroll patients with AECOPD who presented with type 2 respiratory failure(T2RF) requiring noninvasive ventilatory support. This study included adults (aged ≥40 years) diagnosed with Chronic Obstructive Pulmonary Disease (COPD) and admitted for acute exacerbation, specifically those who exhibited T2RF and required noninvasive ventilatory (NIV) support. Patients were excluded if they had concurrent infections other than COPD exacerbation, autoimmune diseases, malignancies, recent surgery, trauma, current immunosuppressive therapy, or chronic kidney or liver diseases, NIV contraindications. The required sample size was determined using an estimated 30% prevalence of NIV requirement among the COPD exacerbation admissions, referencing the hospital's historical data. Adopting a 95% confidence interval and allowing for a 12% margin of error, we determined that a sample of 64 patients would be sufficient to achieve statistical significance. (Fig 1)

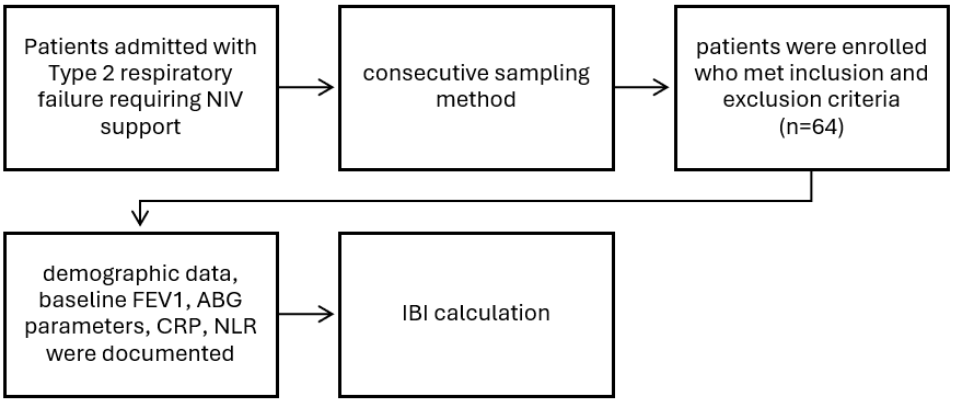


Fig.1. Study flow chart

(NIV- Non-Invasive ventilation, FEV1- Forced Expiratory Volume in 1 second, ABG- Arterial Blood Gas, CRP- C Reactive Protein, NLR- Neutrophil lymphocyte Ratio, IBI- Inflammatory Burden Index)

Upon enrollment, Data collection and analysis medical records will be reviewed to extract data related to detailed demographic information, baseline pulmonary function tests (including Forced Expiratory Volume in 1 second [FEV1]), and arterial blood gas (ABG) parameters (pH, pCO2 (Partial pressure of Carbon dioxide), pO2 (Partial pressure of Oxygen)) were collected. Inflammatory markers, namely C - reactive protein (CRP), and Neutrophil-to-Lymphocyte Ratio (NLR), were recorded. Inflammatory Burden Index (IBI) was calculated using the formula:

IBI=CRP (mg/L) ×Neutrophil count ($\times 10^9$/l)/ Lymphocyte count ($\times 10^9$/l)

This formula was chosen based on the established roles of CRP, neutrophils, and lymphocytes in systemic inflammation and immune response during acute exacerbations of COPD (AECOPD). [12] CRP, an acute-phase reactant, reflects systemic inflammation and correlates with disease severity. Neutrophils indicate immune activation and airway inflammation, while reduced lymphocyte levels are associated with immune suppression and worse prognosis. Multiplying CRP and neutrophils captures the inflammatory burden, while dividing by lymphocyte count accounts for immune dysregulation. This weighted approach makes IBI a robust marker of systemic inflammation, providing a predictive measure for clinical severity and the need for non-invasive ventilation (NIV) in AECOPD patients.

This study distinguishes itself by utilizing unadjusted IBI values, which, unlike normalized values commonly applied in larger epidemiological studies, may obscure acute inflammatory responses pertinent to acute clinical assessment. This choice anticipates offering enhanced predictive insights for immediate clinical application.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY). Descriptive statistics, including mean and standard deviation, were used. The chi-squared test was used to analyze categorical variables. The Mann-Whitney U test was used to compare non-normally distributed continuous variables. Spearman's rank correlation was used to assess relationships between IBI and clinical parameters. The accuracy of IBI in predicting the need for NIV at discharge was assessed through Receiver Operating Characteristic (ROC) curve analysis, with a predefined significance threshold set at $p<0.05$.

2. RESULTS

Table.1: Clinical and Biochemical characteristics of AECOPD with T2RF patients - complete recovery and partial recovery (with NIV)

Variable	Complete Recovery (N=15)	Partial Recovery with NIV (N=49)	p-value
Age (years)	60 ± 19	61 ± 13.5	0.651
C-Reactive Protein (CRP, mg/L)	6.6 ± 4	23.68 ± 67.46	0.001*
Total Leukocyte Count (TC, cells/µL)	7600 ± 2000	12100 ± 5150	0.001*

Neutrophils	66 ± 19.1	79.4 ± 12.65	0.001*
Lymphocytes	19.4 ± 18	11.6 ± 7.9	0.001*
Neutrophil-to-Lymphocyte Ratio (NLR)	3.4 ± 3.15	6.79 ± 6.481	0.001*
Inflammatory Burden Index (IBI)	22.6 ± 27.1	79.4 ± 26	0.001*
pH (arterial blood gas)	7.366 ± 0.062	7.341 ± 0.054	0.041*
pCO_2 (mmHg)	62.5 ± 4.9	63.6 ± 12.7	0.419
pO_2 (mmHg)	66.4 ± 10.3	57.8 ± 21.7	0.070
Pulmonary Hypertension (PHTN, mmHg)	30 ± 10	33 ± 14	0.037*
Baseline FEV_1 (% predicted)	66 ± 22	45 ± 22	0.001*

Median ± Interquartile Range (IQR); Mann whitney U test; *($p<0.05$)

(AECOPD-- Acute Exacerbation of Chronic Obstructive Pulmonary Disease, T2RF- Type 2 Respiratory Failure, NIV- Non-Invasive Ventilation, pCO2-partial pressure of Carbon dioxide, pO2-partial pressure of oxygen, FEV1- Forced Expiratory Volume in 1 second)

Among the 64 patients (mean age: 60 ± 13 years), 46.9% were female and 53.1% were male (Table 1). The clinical and biochemical characteristics of AECOPD with T2RF patients categorized into those who achieved complete recovery and those requiring NIV at discharge. Patients requiring NIV exhibited significantly higher CRP (23.68 ± 67.46 mg/L vs. 6.6 ± 4 mg/L, p=0.001), total leukocyte count (12100 ± 5150 cells/µL vs. 7600 ± 2000 cells/µL, p=0.001), and neutrophil-to-lymphocyte ratio (6.79 ± 6.481 vs. 3.427 ± 3.15, p=0.001). Moreover, the Inflammatory Burden Index (IBI) was significantly elevated in the partial recovery group (79.4 ± 26 vs. 22.6 ± 27.1, p=0.001), highlighting its association with worse clinical outcomes.

Table.2. Comparison of recovery status in AECOPD with T2RF patients by mMRC score, PHTN grade, FEV1

Variable	Complete Recovery (N = 15)	Partial Recovery (with NIV, N = 49)	p-value
mMRC SCORE			
- Score 2	7 (46.7%)	10 (20.4%)	0.121
- Score 3	6 (40.0%)	26 (53.1%)	
- Score 4	2 (13.3%)	13 (26.5%)	
CRP			
- Non-Reactive (NR)	13 (86.7%)	10 (20.4%)	0.001*
- Reactive (R)	2 (13.3%)	39 (79.6%)	
PHTN GRADE			
- Mild	9 (60.0%)	27 (55.1%)	0.056
- Moderate	2 (13.3%)	10 (20.4%)	
- Severe	0 (0%)	9 (18.4%)	
- Normal	4 (26.7%)	3 (6.1%)	
BASELINE FEV_1 (Observed Grade)			
- Mild	0 (0%)	2 (4.1%)	0.008*
- Moderate	12 (80.0%)	15 (30.6%)	

- Severe	3 (20.0%)	28 (57.1%)	
- Very Severe	0 (0%)	4 (8.2%)	

Notes: Chi square test; * shows p<0.05

(AECOPD- Acute Exacerbation of Chronic Obstructive Pulmonary Disease, T2RF- Type 2 Respiratory Failure, mMRC-Modified Medical Research Council, PHTN- Pulmonary Hypertension, FEV1- Forced Expiratory Volume in 1 second, CRP-C Reactive Protein)

Table 2 compared the recovery status of AECOPD with T2RF patients based on mMRC score (Modified Medical Research Council score), PHTN (Pulmonary Hypertension) grade, baseline FEV1. Patients with higher mMRC scores were more likely to require NIV at discharge. Notably, severe PHTN was observed in 18.4% of patients requiring NIV compared to 0% in the complete recovery group (p=0.056). A significant proportion of patients with severe or very severe FEV1 reduction required NIV (p=0.008), underscoring the role of pulmonary function impairment in prolonged ventilation dependency (Table 2).

Table.3. Correlation of variables with IBI

Variable	Inflammatory Burden Index (IBI)	
	r value	p value
mMRC Dyspnea Score (mMRC)	0.333	0.007*
pH (arterial blood gas)	-0.703	0.001*
pCO_2 (mmHg)	0.696	0.001*
pO_2 (mmHg)	0.113	0.376
Pulmonary Hypertension (PHTN, mmHg)	0.103	0.420
Baseline FEV_1 (% predicted)	-0.465	0.001*

Notes: Spearman's rank correlation; * shows p<0.05

(mMRC-Modified Medical Research Council, pCO2-partial pressure of Carbon dioxide, pO2-partial pressure of oxygen, FEV1- Forced Expiratory Volume in 1 second)

(Table 3) Correlation analysis demonstrated a strong positive correlation between IBI and pCO_2 levels (r=0.696, p=0.001), while a negative correlation was observed with pH (r=-0.703, p=0.001) and FEV1 (r=-0.465, p=0.001). This suggests that higher IBI levels are indicative of worsening respiratory function and acid-base imbalance.

Table. 4: Predictive performance of biomarkers for the need for Non-Invasive Ventilation (NIV) at discharge in AECOPD with T2RF patients

Variable	AUC (95% CI)	Predicted Cut-off Value	Sensitivity (95% CI)	Specificity (95% CI)	p-value
CRP	0.87 (0.784-0.964)	11.1	90% (42.86 to 91.84)	79.5% (40-88.3)	0.001 *
Neutrophil-to-lymphocyte ratio (NLR) cells/µL	0.838 (0.725 to 0.918)	4.75	93.3% (68.1 - 99. 8)	73.4% (58.9 - 85. 1)	0.001 *

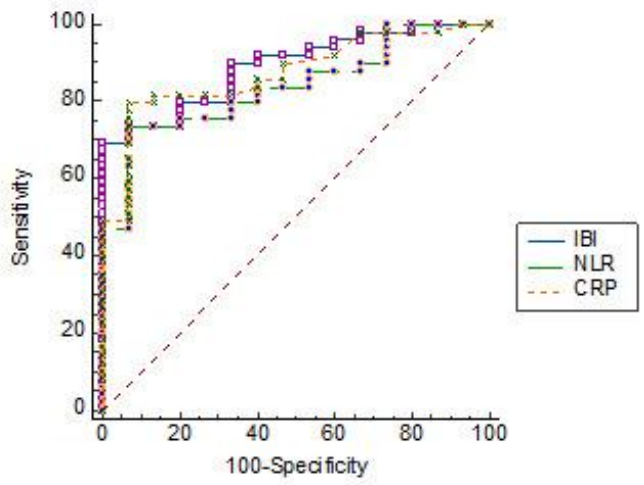
Inflammatory Burden Index (IBI)	0.89 (0.787 to 0.954)	66.7	99% (78.2 - 100 .0)	69.3% (54.6 - 81. 7)	0.001 *

Footnotes: AUC: Area Under the Curve, CI: Confidence Interval; Cut-off Value: Calculated using the Youden Index, which maximizes the difference between sensitivity and 1-specificity. The Youden Index is defined as J = Sensitivity + Specificity – 1; *($p<0.05$)

(AECOPD- Acute Exacerbation of Chronic Obstructive Pulmonary Disease, T2RF- Type 2 Respiratory Failure, CRP- C Reactive Protein)

(Table 4) Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of various biomarkers for NIV requirement. The AUC for IBI was 0.89 (95% CI: 0.787–0.954, p=0.001), with a cut-off value of 75.2, a sensitivity of 99%, and a specificity of 69.3%. Comparatively, CRP and NLR demonstrated AUCs of 0.87 and 0.838, respectively, reinforcing the superior predictive ability of IBI in identifying patients at risk for prolonged NIV dependency (Table 4) (Fig.2).

Fig.2. ROC for various inflammatory markers



IBI- Inflammatory Burden Index, NLR – Neutrophil lymphocyte Ratio, CRP- C Reactive Protein

3. DISCUSSION

This study assessed the prognostic value of the Inflammatory Burden Index (IBI) in predicting non-invasive ventilation (NIV) requirements in acute exacerbations of COPD (AECOPD) with type 2 respiratory failure (T2RF). Patients requiring long-term NIV had significantly higher CRP, total leukocyte count, neutrophil-to-lymphocyte ratio (NLR), and IBI. IBI correlated positively with pCO_2 and negatively with pH and FEV1, reinforcing its role as a strong inflammatory marker. Receiver operating characteristic (ROC) analysis (AUC = 0.89, $p<0.001$) demonstrated IBI's superior predictive value of IBI over NLR for NIV dependency. These findings align with prior research indicating that multiparameter indices provide better prognostic accuracy than individual inflammatory markers. [12]

Systemic inflammation plays a central role in the progression of COPD and the severity of exacerbations. Prior studies have established CRP and NLR as important biomarkers, but their predictive utility remains limited. [13,14] CRP is a well-established acute-phase reactant that reflects systemic inflammation and correlates with the severity of exacerbations (Jing et al., 2016). However, its utility is limited by non-specificity, as elevated CRP levels can be influenced by concurrent infections, cardiovascular diseases, and other inflammatory conditions. [15] Similarly, the NLR is associated with poor outcomes but does not fully capture the complexity of AECOPD-related inflammation.[16] Despite its reliability, NLR lacks specificity in distinguishing COPD-related inflammation from other systemic inflammatory responses. [13, 17] The IBI integrates CRP, neutrophils, and lymphocytes, offering a more comprehensive assessment of the inflammatory burden and enhancing its prognostic relevance.

An elevated IBI reflects increased systemic inflammation, contributing to hypercapnia, impaired gas exchange, and acid-base imbalances. [12] However, pO_2 and pulmonary hypertension (PHTN) did not show significant correlations with IBI in

our study. While PHTN is often associated with severe COPD and systemic inflammation, [18] this study did not find a significant correlation between PHTN and IBI.

Prior studies identified NLR as a key predictor of mortality in AECOPD. Teng et al. (2018) reported NLR >8.130 (AUC: 0.737, sensitivity: 60.5%, specificity: 74.8%) as a strong predictor of 28-day mortality, while Feng et al. (2023) found NLR >14.17 (AUC: 0.802, sensitivity: 76.7%, specificity: 88.9%) linked to 90-day mortality risk. Although CRP has been explored, its predictive value for in-hospital mortality remains inconsistent. [19,20]. These findings align with the present study, where an elevated IBI was significantly associated with NIV dependency, reinforcing its clinical significance. [16,21]

COPD is a progressive inflammatory condition affecting the lungs, strongly associated with tobacco use. The immune system's disruption caused by smoke exposure leads to sustained and elevated inflammation in the lungs, which plays a critical role in the onset of T2RF. [12] Studies suggest that systemic inflammation in COPD may stem from pulmonary inflammation spillover, tissue hypoxia, or immune responses to bacterial infections. Neutrophil recruitment in COPD triggers oxidative stress and protease release, leading to tissue destruction in emphysema and airway remodeling in chronic bronchitis. Elevated NLR reflects increased neutrophil activity, whereas CRP is induced by IL-6 signaling. [12] While NLR and CRP are expected to correlate; some studies have reported variations due to underlying COPD phenotypes. Study by Taylan et al., showed that NLR is significantly higher in COPD exacerbations, higher in stable COPD than in control group. [22]

Existing models, such as the BODE index (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) and the DECAF score (Dyspnea, Eosinopenia, Consolidation, Acidemia, and Atrial Fibrillation), are widely used for COPD risk stratification but lack direct inflammatory measures. [23]. Integrating the IBI into these models could enhance their predictive accuracy by accounting for inflammation in disease progression and treatment response.[24]. Zhu et al. (2024) [12] found that an elevated IBI was associated with increased mortality in chronic inflammatory airway diseases, suggesting its potential use in COPD. Given its predictive value in multiple conditions, IBI's role of IBI in COPD management warrants further investigation.

Early identification of high-risk AECOPD patients using IBI could improve clinical decision-making, resource allocation, and patient outcomes. Timely NIV initiation in patients with high IBI values may help prevent progressive respiratory failure. Future studies should validate IBI's predictive accuracy of IBI in multicenter cohorts and explore its integration into COPD risk models.

While the present study provides strong evidence for IBI as a predictive biomarker, certain limitations must be acknowledged. The single-center design and small sample size may limit the generalizability of the findings, necessitating larger multicenter studies for validation. Potential selection biases may have influenced results due to consecutive sampling.

Furthermore, higher IBI values may be influenced by various other factors beyond systemic inflammation, including infective etiology, microbiological factors, duration of hospital stay, and hospital-acquired pneumonia (HAP). These factors may independently contribute to the systemic inflammatory burden and should be further explored in future studies to assess their impact on IBI's predictive accuracy of the IBI.

Additionally, this study primarily focused on AECOPD patients requiring ventilatory support (GOLD E (Global Initiative for Chronic Obstructive Lung Disease)), whereas IBI could also be evaluated in GOLD A and B COPD patients for earlier identification of those at risk for deterioration. Incorporating IBI into preemptive decision-making and treatment scaling in less severe COPD cases could help optimize early intervention strategies and reduce the risk of disease progression.

Future studies should explore IBI's role of IBI in proactive treatment planning across different COPD phenotypes and assess its integration into existing COPD management frameworks.

4. CONCLUSION

This research highlights IBI as a superior predictor of NIV dependency in AECOPD patients with T2RF, surpassing NLR and CRP in prognostic accuracy. Integrating IBI into clinical practice could enhance early risk stratification and treatment planning, ultimately improving patient management in COPD exacerbations.

Future research should focus on validating IBI in larger, multi-center studies to confirm its clinical utility and integration into COPD prognostic models. Additionally, early prediction using IBI could be extended to GOLD A, B, and E patients, enabling risk stratification across different severity classifications. By incorporating IBI into routine assessments, clinicians may be able to preemptively identify high-risk individuals, personalize treatment approaches, and prevent disease progression. Further studies should explore IBI's role in guiding early interventions, optimizing ventilatory support strategies, and refining COPD management frameworks to improve long-term patient outcomes.

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Conceptualization: Dr Sridhar R, Dr Varshni P V

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Data analysis: Dr Varshni P V

Writing – original draft, review and editing: Dr Muthukumaran L, Dr Varshni P V

Supervision: Dr Meenakshi N, Dr Sridhar R, Dr Muthukumaran L

All authors have read and agreed to the published version of the manuscript

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