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Non-invasive Ventilation Outcome (NIVO) score for predicting in-hospital and late mortality of chronic obstructive pulmonary disease (COPD) patients with acute hypercapnia

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Abstract:

BACKGROUND AND AIM: Mortality and morbidity increase with acute hypercapnic respiratory failure during chronic obstructive pulmonary disease (COPD) exacerbation. Due to the lack of adequate prognostic scoring systems for assessing mortality in patients with acute hypercapnic respiratory failure during COPD exacerbation, we aimed to assess the efficacy of the NIVO score as a predictor of in-hospital and late mortality in COPD patients with acute hypercapnic respiratory failure.

METHODS: This retrospective cross-sectional study was conducted in a tertiary research and training hospital for chest diseases from November 2019 to November 2021, and included patients with COPD who were hospitalized with exacerbation requiring assisted ventilation. The patients' demographic characteristics, laboratory data, and clinical information were collected from the hospital database. Patients were classified according to their NIVO score. In-hospital and late mortality rates were recorded.

RESULTS: The study included 250 COPD patients with acute hypercapnic respiratory failure. The majority of patients (42%) classified according to the NIVO score were in the moderate-risk group. The intubation rate due to Non-Invasive Mechanical Ventilation (NIMV) failure in the high-risk group based on the NIVO score was 38.8%, while the rates in the moderate- and low-risk groups were 9.5% and 8%, respectively. The high-risk group had a significantly higher risk of intubation compared to the moderate- and low-risk groups ($p<0.001$). Increased risk levels according to the NIVO score were associated with significantly higher in-hospital and late mortality rates ($p<0.001$).

CONCLUSIONS: The novel and easy-to-use NIVO score is important for predicting the prognosis of COPD patients with exacerbation requiring assisted ventilation.

Keywords:

Acidosis, chronic obstructive pulmonary disease (COPD) exacerbation, prognosis, respiratory failure, score

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Introduction

Mortality and morbidity increase with acute hypercapnic respiratory failure during chronic obstructive pulmonary disease (COPD) exacerbation.[1,2] Non-invasive mechanical ventilation (NIMV) prevents intubation, treatment failure, and mortality when administered in the early phase of acute hypercapnic respiratory failure, before severe acidosis occurs.[3] Non-invasive mechanical ventilation administration reduces mortality by up to 46% in cases of acute hypercapnic respiratory failure.[4] Compared to invasive mechanical ventilation, NIMV is associated with fewer complications and shorter hospital and intensive care unit (ICU) stays.[5] However, NIMV failure still accounts for up to 20% of COPD exacerbations.[6,7] Researchers have proposed various scoring systems, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[8] the COPD and Asthma Physiology Score (CAPS),[9] the Confusion, Urea, Respiratory rate, Blood pressure-65 (CURB-65),[10] the Heart rate, Acidosis, Consciousness, Oxygenation, Respiratory rate (HACOR)[11] and the Dyspnea, Eosinopenia, Consolidation, Acidemia, and Atrial Fibrillation (DECAF) score,[12,13] to assess the risk of NIMV failure and to aid in decision-making for NIMV initiation. Unfortunately, these scoring systems are not easy to apply upon hospital admission and are not specific for assessing the mortality and morbidity of in-hospital COPD patients; thus, they are not routinely used. The Non-Invasive Ventilation Outcome (NIVO) score, developed by Hartley et al.,[14] has been shown to successfully predict in-hospital mortality in patients with acute COPD exacerbation and to help identify patients who may require strict monitoring and mechanical ventilation during their hospital stay.

In our study, we aimed to investigate the predictive accuracy of the NIVO score for in-hospital and late mortality in patients with COPD admitted to our hospital with acute hypercapnic respiratory failure, with or without acidemia at hospital admission.

Materials and Methods

Between November 2019 and November 2021, patients with previously diagnosed COPD who were admitted to our emergency department, hospitalized with acute hypercapnic respiratory failure, and treated with non-invasive mechanical ventilation were included in this retrospective cross-sectional study. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the from Sureyyapasa Chest Diseases and Chest Surgery Non-Interventional Clinical Research Ethics Committee (Approval Number: 116.2017.R-243, Date: 03.03.2022). As it was a retrospective study, informed consent was not obtained.

Chronic obstructive pulmonary disease diagnoses were previously established by a physician who evaluated airflow obstruction using spirometry; patients with a forced expiratory volume in 1 second (FEV_1) of 70% predicted or less, and an FEV_1 to forced vital capacity ratio of 70% or less were determined to have COPD. Spirometry testing was not conducted for either confirmation or new diagnoses of COPD. Hypercapnic/hypoxemic respiratory failure was defined as a partial pressure of carbon dioxide ($PaCO_2$) greater than 45 mmHg and a partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio less than 300, while hypercapnic respiratory failure alone was defined as a $PaCO_2$ greater than 45 mmHg and a PaO_2/FiO_2 ratio above 300. Patients with a $PaCO_2$ greater than 45 mmHg with normal (22–26 mEq/L) or elevated bicarbonate (HCO_3) levels, as well as patients with metabolic acidosis accompanied by hypercapnia according to Winter's formula, were included in the study.

Inclusion criteria were previously diagnosed COPD patients with acute hypercapnic respiratory failure receiving NIMV, aged 35 years or older, and with a smoking history of at least 10 pack-years.

The exclusion criteria were as follows:

1. Patients with an illness that restricts their expected lifespan to less than one year (e.g., metastatic carcinoma);
2. Patients with positive Coronavirus Disease 2019 (COVID-19) polymerase chain reaction (PCR) results;
3. Patients with mobility issues (e.g., hemiplegia, paraplegia, lower extremity amputation, etc.).

Among 4,925 patients admitted to the emergency department and who received NIMV, 250 patients meeting the inclusion criteria were included in our study. Data were collected from the hospital database and patient records. Patient information, including demographics, duration of COPD, smoking history, comorbid conditions, use of oxygen concentrators and bilevel positive airway pressure (BiPAP), electrocardiogram, posterior-anterior chest

Table 1: Non-invasive ventilation outcome (NIVO) and modified NIVO scores

NIVO score		Modified NIVO score	
Atrial fibrillation	1 point	Atrial fibrillation	1 point
Consolidation on chest X-ray	1 point	Consolidation on chest X-ray	1 point
Glasgow coma score≤14	1 point	Glasgow coma score≤14	1 point
Arterial pH<7.25	1 point	Arterial pH<7.25	1 point
Time from admission to acidemia >12 hours	2 points	Acidemia duration from admission >12 hours	2 points
Extended medical research council (eMRC) dyspnea score 5a	2 points	eMRC dyspnea score 5a	2 points
eMRC dyspnea score 5b	3 points	eMRC dyspnea score 5b	3 points
Total	9 points	Total	9 points

5a: Housebound patients able to wash and dress independently, 5b: Housebound patients unable to wash and dress independently due to dyspnea. 0–2 points: Low risk, 3–4 Points: Medium risk, 5–6 points: High risk; 7–9 points: Very high risk

X-ray, extended Medical Research Council Dyspnea (MRCD) score, blood gas analysis, hematological and biochemical parameters, in-hospital and late mortality, and rehospitalization within 90 days after hospital discharge were gathered.

The NIVO score is based on six parameters: extended MRCD score, time from admission to acidemia >12 hours, pH<7.25, atrial fibrillation, Glasgow Coma Score≤14, and chest X-ray consolidation (Table 1).[14] Observations in our clinical practice revealed that most patients with acute hypercapnic respiratory failure presented with acidosis upon admission to the emergency department, resulting in a score of 0 for the "time from admission to acidemia >12 hours" parameter. To address this discrepancy, we developed a modified NIVO score, changing the parameter to "acidemia duration from admission >12 hours" (Table 1). An extended MRC dyspnea score of 5a indicates that a patient is too breathless to leave the house without assistance, while a score of 5b indicates the patient is also unable to wash and dress independently. The modified NIVO score uses the same point values for each parameter as the original NIVO score, as both scoring systems exhibited similar receiver operating characteristic (ROC) curves.

Extended MRC dyspnea scores were retrieved from the hospital database, patient records, and nursing records taken at hospitalization, which contain a similar questionnaire to the extended MRCD (eMRCD) score.

In-hospital mortality defined as mortality during hospital stay and late mortality defined as mortality at 90 days after hospital admission.

The presence of chest radiograph consolidation was determined in the following order of priority: interpretation by the attending senior clinician, followed by researcher assessment. Differential diagnoses were made by analyzing patients' epicrisis summaries and laboratory parameters.

Atrial fibrillation diagnosis was confirmed through patient records, baseline electrocardiograms (ECG) taken at hospitalization, and/or cardiology consultations conducted during the hospital stay.

Statistical Analysis

Statistical analysis was performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). To compare two groups, Student's t-test was used for data with a Gaussian distribution, and the Mann-Whitney U test was applied to non-normally distributed data. Variables related to ICU transfer, intubation, and mortality were compared using the Chi-Square test. Continuous parameters were analyzed with Spearman correlation, while categorical parameters were analyzed using the Pearson Chi-Square test and Fisher's exact test. A p value of 0.05 was considered statistically significant.

The sample size was calculated using G Power analysis version 3. The required sample size was 220, with a medium effect size, 95% power, and an α error probability of 0.05.

Results

In this study, 167 (66.8%) of the 250 patients were male. The mean age of the patients was 69.4 (±9.3) years, and the median cigarette exposure was 50 (range: 30–60) pack-years. Of the patients, 190 (76%) had oxygen concentrators, and 143 (57.2%) had a BiPAP device. The median hospital stay was 10 days (min: 2, max: 52).

Among the 250 patients, 138 (55.2%) had hypertension, 88 (35.2%) had coronary artery disease, 72 (28.8%) had type 2 diabetes mellitus, 64 (25.6%) had bronchiectasis, 52 (20.8%) had congestive heart failure, 41 (16.4%) had post-tuberculosis sequelae, 35 (14%) had atrial fibrillation, 19 (7.6%) had malignancy, 19 (7.6%) had chronic renal disease or failure, 14 (5.6%) had a history of pulmonary embolism, and six (2.4%) had a history of cerebrovascular accidents.

Patients were classified according to the NIVO and modified NIVO scores, with a higher number of patients found in the moderate-risk group (Table 2).

Table 2: Distribution of patients by risk category for non-invasive ventilation outcome (NIVO) and modified NIVO scores

Risk	n	%
NIVO score		
Low risk	88	35.2
Moderate risk	105	42.0
High risk	49	19.6
Very high risk	8	3.2
Modified NIVO score		
Low risk	83	33.2
Moderate risk	108	43.2
High risk	53	21.2
Very high risk	6	2.4

Among the 250 patients, 145 (58%) had acidosis at admission. The median pH was 7.33 (range: 7.28–7.37), and the median partial pressure of carbon dioxide (pCO_2) was 62.45 mmHg (range: 54.87–73.02 mmHg).

During their hospital stay, 40.2% of the patients (n=70) were transferred to the ICU. Due to NIMV failure, 15.6% of the patients (n=39) required intubation. In-hospital mortality was 13.2% (n=33), and late mortality was 20% (n=50). Of the 217 patients discharged from the hospital, 79 (36.4%) were rehospitalized within 90 days.

Increased risk levels according to both NIVO and modified NIVO scores were associated with significantly higher in-hospital and late mortality (Table 3).

The intubation rate due to NIMV failure in the high-risk group based on the NIVO score was 38.8% (n=19), while the rates in the moderate- and low-risk groups were 9.5% (n=10) and 8% (n=7), respectively. The high-risk group had a significantly higher risk of intubation compared to the moderate- and low-risk groups (p<0.001). Similarly, using the modified NIVO score, the intubation rate in the high-risk group was significantly greater than in the moderate- and low-risk groups (p<0.001) (Table 3).

A statistically significant, weak positive correlation was observed between hospital stay and the NIVO score (Rho=0.144, p=0.024); however, no statistically significant correlation was found between the modified NIVO score and hospital stay (p=0.075) (Table 4).

Both NIVO and modified NIVO scores were significantly higher in patients who were discharged from the hospital but required rehospitalization within 90 days (p=0.029 and p=0.004, respectively) (Table 5).

According to the univariate analysis, in-hospital and late mortality were significantly higher in patients with longer hospital stays, longer durations since COPD diagnosis, and advanced age. In-hospital and late mortality were significantly higher in patients with elevated

Table 3: Relationships between in-hospital mortality, late mortality, noninvasive mechanical ventilation (NIMV) failure, and risk categories of non-invasive ventilation outcome (NIVO) and modified NIVO scores

	In-hospital mortality				Late mortality				Intubation			
	Total NIVO		Total modified NIVO		Total NIVO		Total modified NIVO		Total NIVO		Total modified NIVO	
	n	%	n	%	n	%	n	%	n	%	n	%
Low risk	6	6.8	5	6.0	10	11.4	10	12.0	7	8.0	5	6.0
Moderate risk	9	8.6	11	10.2	14	13.3	17	15.7	10	9.5	14	13.0
High risk	14	28.6*	15	28.3**	22	44.9*	20	37.7**	19	38.8*	18	34.0*
Very high risk	4	50.0	2	33.3	4	50.0	3	50.0	3	37.5	2	33.3
Total	33	13.2	33	13.2	50	20.0	50	20.0	39	15.6	39	15.6

*: Fisher's exact test, p<0.001, **: Fisher's exact test, p=0.001

Table 4: Relationship between hospital stay and non-invasive ventilation outcome (NIVO) and modified NIVO scores

	Hospital stay (days)
NIVO	
Rho	0.144
p	0.024
n	249
Modified NIVO	
Rho	0.113
p	0.075
n	249

Spearman's Correlation

Table 5: Relationship between rehospitalization and non-invasive ventilation outcome (NIVO) and modified NIVO scores

	Rehospitalization within 90 days after discharge	
	Median	p
NIVO	3 (2–4)	0.029*
Modified NIVO	4 (2–5)	0.004*

*: Mann-Whitney U Test

C-reactive protein (CRP), procalcitonin, and blood urea nitrogen (BUN) levels, as well as lower hemoglobin and eosinophil counts (Table 6).

Discussion

In our study, high-risk patients according to the NIVO score had significantly higher in-hospital and late mortality rates than those in the moderate- and low-risk groups. An increased modified NIVO score was also associated with increased mortality, similar to the original NIVO score. However, there was no significant association between mortality and very-high-risk status in either scoring system, which may be attributed to the low number of patients in the very-high-risk group. Our findings are consistent with the original NIVO study published by Hartley et al.[14] As there are no other studies in the literature evaluating mortality in acute hypercapnic respiratory failure during COPD exacerbations using the NIVO score in English publications, our study provides new insights in this field.

A study by Peng et al.[15] evaluating risk factors for in-hospital mortality in COPD exacerbation patients revealed results consistent with our finding that deceased patients had longer hospital stays, higher ICU admission rates, and greater need for invasive ventilation. The same study also found that mortality in COPD exacerbations increases with age, with age over 80 years identified as an independent risk factor for mortality. In our study, we similarly found that in-hospital mortality was higher in patients with advanced age and longer COPD duration. This trend may be attributed to the increased annual decline in FEV_1 in COPD patients compared to the general population. Increased comorbidities at advanced age may also contribute to the higher mortality risk.

We found that the prevalence of atrial fibrillation, a component of the NIVO score, was 14%. In a study by Konecny et al.,[16] the prevalence of atrial fibrillation in sta-

Table 6: Baseline characteristics of patients and their relationship with in-hospital and late mortality

	In-hospital mortality		Late mortality (90 days)	
	Median (p25-p75)	p*	Median (p25-p75)	p*
Age (years)	77.0 (68.0–85.0)	**<0.001**	74.0 (67.0–83.0)	**<0.001**
Cigarette smoking (pack/year)	50.0 (40.0–60.0)	0.248	50.0 (35.0–60.0)	0.403
COPD duration (years)	10.0 (8.0–12.0)	**0.047**	10.0 (8.0–10.0)	**0.014**
Hospital stay (days)	23 (14–33)	**<0.001**	16 (10–27)	**<0.001**
WBC (10^9/L)	14.61 (9.64–18.69)	**0.001**	12.23 (8.85–16.20)	**0.025**
Hb (g/dL)	11.4 (9.8–13.5)	**0.004**	11.3 (9.8–13.3)	**<0.001**
PLT (10^9/L)	266.0 (209.0–379.0)	0.153	275.5 (216.0–341.0)	0.053
Eos# (10^9/L)	0.02 (0.01–0.12)	**0.011**	0.03 (0.01–0.13)	**0.007**
CRP (mg/dL)	67.45 (21.85–114.05)	**0.001**	54.90 (13.95–102.20)	**0.011**
Procalcitonin (ng/dL)	0.304 (0.166–1.060)	**<0.001**	0.203 (0.072–0.497)	**<0.001**
BUN (mg/dL)	54.0 (35.0–70.0)	**0.021**	48.5 (35.0–66.0)	**0.014**
Creatinine (mg/dL)	0.85 (0.64–1.05)	0.328	0.75 (0.62–1.05)	0.968

*: Mann-Whitney U test. COPD: Chronic obstructive pulmonary disease, WBC: White blood cell count, Hb: Hemoglobin, PLT: Thrombocyte count, Eos#: Eosinophil count, CRP: C-reactive protein, BUN: Blood urea nitrogen

ble COPD patients was found to range between 4.7% and 15%, reaching up to 30% in patients with severe COPD. Various studies have also shown that patients with heart failure and atrial fibrillation exhibit poorer exercise capacity and reduced air exchange function in their lungs due to the high ventricular rate caused by atrial fibrillation.[17,18] Furthermore, past research has identified a temporary increase in atrial fibrillation incidence during COPD exacerbations, attributed to factors such as hypoxia-related mechanisms, inflammation, changes in the autonomic nervous system, and the use of beta-adrenergic mimetic agents.[19] The presence of consolidation on lung X-ray, another component of the NIVO score for predicting mortality, plays an important role in identifying infections and determining the frequency of steroid use during exacerbations in COPD patients. Studies have shown that corticosteroid use is associated with an increased risk of pneumonia and mycobacterial infection.[20,21] Additionally, pneumonia can exacerbate preexisting tissue hypoxia caused by respiratory failure during COPD exacerbations. Shukla et al.[22] reported that tissue hypoxia facilitates bacterial colonization through various molecular mechanisms, leading to an increased frequency of exacerbations. In this context, infection-related COPD exacerbations may create a cycle in which tissue hypoxia promotes bacterial colonization, while bacterial colonization further contributes to exacerbations, potentially accelerating disease progression and increasing mortality risk.

The validation study of the NIVO score conducted by Hartley et al.[14] with a cohort of 733 participants from 10 centers found that previous NIMV and home ventilator usage was up to 44.6%. However, in our study, the use of previous NIMV among acute hypercapnia patients admitted to emergency services was more frequent, at 57.2%. This may have impacted the pH levels of patients upon hospital admission. In our study, 58.5% of patients experienced respiratory acidosis at hospital admission. This finding suggests that higher rates of NIMV usage may have led to delayed emergency admission. Consequently, these patients may have experienced a delayed response to noninvasive ventilation therapy. This situation implies that acidemia lasting longer than 12 hours after hospital admission may predict mortality in addition to the NIVO score, even though it conflicts with one of the original NIVO score components, "time from admission to acidemia >12 hours." To address this discrepancy, a modified NIVO score was proposed, in which this component was revised to "acidemia duration from admission longer than 12 hours."

A study evaluating the effect of severe acidosis (pH<7.25) on NIMV failure, compared to patients without severe acidosis in a cohort of 969 patients with COPD exacerbation, acute cardiogenic pulmonary edema, and obstructive sleep apnea, reported that patients with severe acidosis required a longer time to reach normal pH and had extended ICU stays.[23] These findings underscore the importance of the pH<7.25 parameter in the NIVO score.

According to univariate analysis between in-hospital mortality and laboratory findings, C-reactive protein, procalcitonin, and blood urea nitrogen levels, as well as low hemoglobin and eosinophil levels, were significantly correlated. The most common cause of COPD exacerbation is bacterial infection, which is associated with poor prognosis, explaining the correlation between elevated infection markers and mortality. A study conducted by Mendy et al.[24] in 2018 found that high CRP levels, high neutrophil counts, and low eosinophil counts were associated with mortality and poor prognosis, findings that are consistent with our study. These outcomes may reflect a poor response to acute exacerbation therapy in patients with low eosinophil counts, leading to increased mortality, as eosinophil counts impact the steroid treatment response in COPD patients. A study of 275 patients by Karauda et al.[25] reported that eosinopenia and lymphocytopenia predicted in-hospital mortality with a sensitivity of 100% and specificity of 84.4%. Additionally, in the same study, surviving patients had longer hospital stays. Our study did not examine the correlation with lymphocytopenia as lymphocyte counts were not recorded, but the presence of eosinopenia was significantly correlated with both in-hospital and late mortality, which supports previous evidence. However, a specific cutoff value could not be identified. Peng et al.[15] also observed high leukocyte counts and low hemoglobin (Hb) levels in the laboratory findings of patients who died from COPD exacerbation. In our study, it was unsurprising that high BUN levels were significantly associated with in-hospital and late mortality, as the CURB-65 score has previously demonstrated a relationship between BUN levels and mortality.[10]

Limitations

One limitation of our study is its single-center design. However, our hospital has a high patient capacity, with a great number of patient admissions and numerous beds, as it is one of the four main pulmonary medicine special-

ty hospitals in Türkiye. For this reason, we believe our findings can be generalized to the broader population.

Another limitation of our study is its retrospective design. However, we believe the dataset is reliable, as meticulous hourly records of critically ill patients are available.

Conclusion

Both in-hospital and late mortality rates increased in correlation with higher NIVO and modified NIVO scores. High-risk patients, as classified by both NIVO and modified NIVO scores, had significantly higher in-hospital and late mortality rates. Additionally, both scoring systems were effective in predicting NIMV failure. Our findings support previous literature, indicating that the novel and user-friendly NIVO score is a valuable tool for predicting the prognosis of COPD patients with acute hypercapnic respiratory failure. We suggest that the modified NIVO score, with the parameter "acidemia duration from admission longer than 12 hours," may be more useful for patients with assisted ventilation use and acidosis at admission.

Ethics Committee Approval

The study was approved by the Sureyyapasa Chest Diseases and Chest Surgery Non-interventional Clinical Research Ethics Committee (No: 116.2017.R-243, Date: 03/03/2022).

Authorship Contributions

Concept – S.Y.Y., M.Ö.A., C.H.K.Y., M.A., D.E.; Design – S.Y.Y., M.Ö.A., C.H.K.Y., M.A., D.E.; Supervision – S.Y.Y., M.Ö.A., C.H.K.Y., M.A., D.E.; Funding – S.Y.Y., M.Ö.A., M.A.; Materials – S.Y.Y., M.Ö.A.; Data collection &/or processing – S.Y.Y., M.Ö.A., D.E.; Analysis and/or interpretation – S.Y.Y., C.H.K.Y., D.E.; Literature search – S.Y.Y., M.Ö.A., D.E.; Writing – S.Y.Y., D.E.; Critical review – S.Y.Y., M.Ö.A., C.H.K.Y., M.A., D.E.

Conflicts of Interest

There are no conflicts of interest.

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