# The noninvasive ventilation outcomes score in patients requiring NIV for COPD exacerbation without prior evidence of airflow obstruction

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**The NIVO score was validated in patients with known airflow obstruction on spirometry. This study shows it has good discrimination (AUROC 0.724) in patients clinically treated for AECOPD but without prior spirometry confirming the diagnosis.** https://bit.ly/3KDvMzu

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## Abstract

***Introduction*** Exacerbation of COPD complicated by respiratory acidaemia is the commonest indication for noninvasive ventilation (NIV). The NIV outcomes (NIVO) score offers the best estimate of survival for those ventilated. Unfortunately, two-thirds of cases of COPD are unrecognised, and patients may present without COPD having been confirmed by spirometry.

***Methods*** In the 10-centre NIVO validation study there was no pre-admission spirometry in 111 of 844 consecutive patients (termed "clinical diagnosis" patients). We compared the performance of the NIVO, DECAF and CURB-65 scores for in-hospital mortality in the clinical diagnosis cohort. Usual clinical practice was not influenced, but confirmation of COPD in the year following discharge was captured.

***Results*** In the clinical diagnosis cohort, in-hospital mortality was 19.8% and rose incrementally across the NIVO risk categories, consistent with the NIVO validation cohort. NIVO showed good discrimination in the clinical diagnosis cohort: area under the receiver operating curve 0.724, *versus* 0.79 in the NIVO validation cohort. At 1 year after discharge, 41 of 89 clinical diagnosis patients had undertaken diagnostic spirometry; 33 of 41 had confirmation of airflow obstruction (forced expiratory volume in 1 s/(forced) vital capacity <0.7), meaning the diagnosis of COPD was incorrect in 19.5% of cases.

***Discussion*** These data support the use of the NIVO score in patients with a "clinical diagnosis" of COPD. NIVO can help guide shared decision-making, assess risk-adjusted outcomes by centre and challenge prognostic pessimism. Accurate diagnosis is critical to ensure that acute and long-term treatment is optimised; this study highlights failings in the follow-up of such patients.

## Introduction

Acute exacerbation of COPD (AECOPD) is one of the most common causes of emergency admission to hospital in the United Kingdom. Approximately 20% of cases are complicated by respiratory acidaemia, with most requiring assisted ventilation, usually administered noninvasively (NIV). The National Confidential Enquiry into Patient Outcomes and Death found that mortality in those receiving NIV for AECOPD was over 25% [1]. In the United Kingdom, around 2 million people with COPD are undiagnosed and 85% of patients have had missed opportunities for diagnosis by the time they are diagnosed [2, 3]. Most patients with COPD are diagnosed late within the natural history of the disease, some only after hospitalisation requiring ventilation [4]. The NIV outcomes (NIVO) score (table 1) is a simple prognostic clinical tool, validated in patients with exacerbations of COPD who require assisted ventilation to predict inpatient mortality [5]. The NIVO score was developed and validated in patients with an existing diagnosis of COPD confirmed by pre-admission airflow obstruction (forced expiratory volume in 1 s ($FEV_1$)/(forced) vital

capacity ((F)VC) <0.70); it has excellent discrimination, with an area under the receiver operating curve (AUROC) of 0.79 and is well calibrated. Calculation of the NIVO score has been incorporated into the British Thoracic Society's respiratory support unit's national audit to facilitate benchmarking between units and assessment of predicted *versus* observed outcomes in AECOPD patients requiring NIV.

However, national audits of COPD care in the United Kingdom have consistently shown that fewer than 50% of patients admitted to hospital for AECOPD have spirometry available to the treating clinician [6]. Conversely, more than one in eight patients hospitalised with presumed AECOPD have no evidence of airflow obstruction on recorded spirometry [6]. Misdiagnosis of COPD in respiratory failure is common, particularly in patients with obesity hypoventilation syndrome (OHS) [7]. In this context, it is likely that the NIVO score will be calculated in patients who present to hospital and are treated with assisted ventilation for "presumed AECOPD"; such patients may have a true underlying diagnosis of COPD but have never had diagnostic spirometry performed or alternatively, may not actually have COPD. The NIVO score is not yet validated in these patients. Furthermore, an incorrect diagnosis of COPD is likely to lead to harmful and expensive therapy, while in true COPD, there is a high but modifiable risk of readmission and death [8]. There is an urgent need to confirm the diagnosis and optimise therapy.

In this study, our primary aim was to assess the utility of the NIVO score in patients treated with NIV for presumed AECOPD complicated by respiratory acidaemia, but who had no evidence of pre-admission spirometry to confirm the diagnosis of COPD; we termed this cohort "clinical diagnosis" (CD) patients. We additionally aimed to assess the number of such patients who subsequently had diagnostic spirometry performed, and to compare patient characteristics of the CD group of patients to those included in the NIVO score validation cohort [5].

The components of the NIVO score (see table 1) are as follows: chest radiograph consolidation (1 point), Glasgow Coma Scale score 14 or less prior to ventilation (1 point), any history of atrial fibrillation prior to ventilation, even if in sinus rhythm at the initiation of ventilation (1 point), pH <7.25 prior to ventilation (1 point), time elapsed between arrival at hospital to development of respiratory acidaemia >12 h (2 points), and pre-admission extended medical research council dyspnoea score 5a or 5b (2 or 3 points respectively). The maximum possible NIVO score is 9, which provides an estimate of in-hospital mortality.

## Methods

Ten UK hospitals prospectively recruited unique, consecutive patients ventilated for AECOPD complicated by respiratory acidaemia (The NIVO Study; ISRCTN22921168) between October 2016 and February 2018, from which the NIVO score was validated [5]. Within the main NIVO study, a subpopulation of CD patients without prior spirometry but meeting all other selection criteria were identified in tandem. Inclusion criteria were age ⩾35 years, ⩾10 pack-year history of smoking, a primary clinical diagnosis of AECOPD, absence of pre-admission spirometry confirming airflow obstruction, treatment with assisted ventilation for respiratory acidaemia (pH<7.35, $P_{aCO_2}$>6.5kPa). Exclusion criteria were previous inclusion in the study, or other disease expected to limit life to <1 year. The CD group characteristics were compared with those in the NIVO study validation cohort (with pre-admission obstructive spirometry, here termed "confirmed COPD"). The validated NIVO score was then calculated in the CD group and discrimination of the score was assessed and compared with the DECAF and the CURB-65 scores [9, 10].

Hospital notes, lung function databases and primary care records were searched thoroughly for spirometry results. Twelve months following admission, a repeat search was performed on CD patients to see whether spirometry had subsequently been performed.

**TABLE 1** The noninvasive ventilation outcomes (NIVO) score

| NIVO score | Points |
|---|---|
| Chest radiograph consolidation | 1 |
| Glasgow Coma Scale ⩽14 | 1 |
| Atrial fibrillation | 1 |
| pH <7.25 | 1 |
| Time to acidaemia >12 h | 2 |
| Extended Medical Research Council Dyspnoea Score 5a | 2 |
| Extended Medical Research Council Dyspnoea Score 5b | 3 |
| Total | 9 |

Comparisons between patients with CD and confirmed COPD were made with a Fishers' exact, Mann–Whitney U or t-test as appropriate. Discrimination of the NIVO score and comparisons with other models were performed by AUROC analysis and statistical differences between these were assessed using the method of DeLong [11]. For variables with <20% missing values, data were assumed to be missing at random and imputed using the expectation-maximisation algorithm. Analyses were performed using IBM SPSS version 25. Full details of the NIVO score derivation and validation regression analyses are available in the original *European Respiratory Journal* publication [5].

## Results

Of 844 patients recruited, 111 (13.2%) had no record of spirometry prior to admission. Compared with confirmed COPD patients, CDs had similar comorbidity, blood gas results, time to acidaemia and mortality. CDs had less-severe, stable-state dyspnoea, higher median body mass index (BMI), were less likely to be on long-term oxygen therapy and had more confusion (table 2). The proportion of patients with severe obesity (BMI ⩾40.0) was statistically similar in both groups.

### *Inpatient mortality and the NIVO score*

CD patients demonstrated an incremental inpatient mortality as the NIVO score risk group increased, in a similar pattern to confirmed COPD patients (table 3).

The NIVO score had numerically lower discrimination in CD patients (AUROC 0.724 (0.598–0.851) than in confirmed COPD patients (NIVO score validation cohort AUROC 0.79 (0.75–0.83)) [5]. There was no significant difference between the AUROCs of the NIVO, DECAF or CURB-65 scores in the CD population (figure 1 and table 4).

### *Subsequent lung function testing*

Of 89 CD patients surviving to discharge, 41 (46.1%) had diagnostic spirometry performed over the next 12 months. Of those, 33 patients (80.5%) had COPD confirmed ($FEV_1$/(F)VC ratio <70%). Two patients had incomplete results ($FEV_1$ measured without vital capacity) and are not counted as having "diagnostic spirometry". Post-admission spirometry results from CD patients, performance status and BMI compared with confirmed COPD patients is shown in table 5. At 12 months, 62.9% (56 of 89) of CD patients either

**TABLE 2** Comparisons of "confirmed COPD" and "clinical diagnosis" patients

| | Clinical diagnosis | Confirmed COPD | p-value |
|---|---|---|---|
| **Subjects, n** | 111 | 733 | |
| **Age, years, mean±SD** | 69.6±10.9 | 70.5±9.3 | 0.34 |
| **Female** | 58 (52.3) | 427 (58.3) | 0.26 |
| **White** | 108 (97.3) | 718 (98.0) | 0.72 |
| **eMRCD score** | 4 (4–5a) | 5a (4–5a) | **0.0019** |
| **Unable to leave house unassisted**[#] | 48 (43.2) | 411 (56.1) | **0.01** |
| **BMI, kg·m$^{-2}$, mean±SD** | 27.4±8.7 | 25.5±8.0 | **0.022** |
| **BMI ⩾40.0 kg·m$^{-2}$** | 9 (8.1) | 38 (5.2) | 0.26 |
| **On LTOT** | 15 (13.5) | 210 (28.6) | **0.0005** |
| **Comorbidity** | | | |
| Left ventricular systolic dysfunction | 19 (17.1) | 103 (14.1) | 0.38 |
| Depression | 25 (22.5) | 173 (23.6) | 0.90 |
| **Admission related** | | | |
| Atrial fibrillation up to ventilation | 18 (16.2) | 143 (19.5) | 0.52 |
| Confusion | 44 (40) | 181 (25.4) | **0.0019** |
| Chest radiography consolidation | 41 (37.3) | 279 (38.1) | 0.92 |
| pH at decision to ventilate | 7.26 (7.20–7.29) | 7.27 (7.22–7.30) | 0.18 |
| Base excess at decision to ventilate | 3.9 (−0.3–8.5) | 3.8 (0.0–8.4) | 0.82 |
| Minutes from admission to NIV decision ABG | 126 (34–587) | 137 (41–767) | 0.60 |
| Acidosis ⩾12 h from admission | 25 (22.5) | 186 (25.4) | 0.56 |
| DECAF score | 2 (2–3) | 3 (2–3) | 0.49 |
| Inpatient mortality | 22 (19.8) | 147 (20.1) | 1.00 |

Data are presented as n (%) or median (interquartile range), unless stated otherwise. eMRCD: Extended Medical Research Council Dyspnoea Score; BMI: body mass index; LTOT: long-term oxygen therapy; NIV: noninvasive ventilation; ABG: arterial blood gas; DECAF: dyspnoea, eosinopenia, consolidation, acidaemia and atrial fibrillation. [#]: defined as an eMRCD score of 5a or 5b. Statistically significant differences are shown in bold.

**TABLE 3** Risk groups by noninvasive ventilation outcomes (NIVO) score in the clinical diagnosis population

| NIVO score risk group | n | Clinical diagnosis cohort inpatient mortality (%) | Confirmed COPD inpatient mortality (NIVO validation data) (%) [5] |
|---|---|---|---|
| **Low (0–2)** | 53 | 9.4 | 5.0 |
| **Medium (3–4)** | 37 | 18.9 | 16.8 |
| **High (5–6)** | 19 | 42.1 | 41.2 |
| **Very high (7–9)** | 2 | 100 | 71.4 |

did not have confirmation of COPD (no spirometry) or did not have COPD (no airflow obstruction). When spirometry was completed, the diagnosis of COPD was incorrect in 19.5% of cases.

## Discussion

In the NIVO study, a substantial minority of patients did not have a prior spirometry-confirmed diagnosis of COPD. These "CD" patients had a better pre-admission, stable-state functional status, but similar overall in-hospital mortality to those with diagnosed COPD, whereas mortality was higher than expected in the CD low-risk NIVO group. This could, in part, be due to under optimisation pre-admission, misdiagnosis or a more severe acute illness precipitating respiratory acidaemia.

The NIVO score demonstrated a stepwise increase in mortality across the NIVO risk groups in CD patients. Approximately 50% of these patients were low risk and 81% were low–moderate risk; broadly similar to that seen in the "confirmed COPD" patients from the NIVO score validation cohort [5].

The NIVO score offers a good prediction of inpatient mortality in the cohort of patients treated for AECOPD with assisted ventilation, but who have no prior spirometry to confirm diagnosis. The AUROC of NIVO in this group, 0.724, is numerically higher than either the DECAF or CURB-65 scores, though no statistical difference between these values was demonstrated. The NIVO score may be less discriminative in CD patients compared with those with confirmed COPD (AUROC=0.79), although the confidence intervals are wide with a substantial overlap. Nonetheless, the NIVO score could be utilised to challenge prognostic pessimism and improve shared decision-making around ventilation in this cohort of

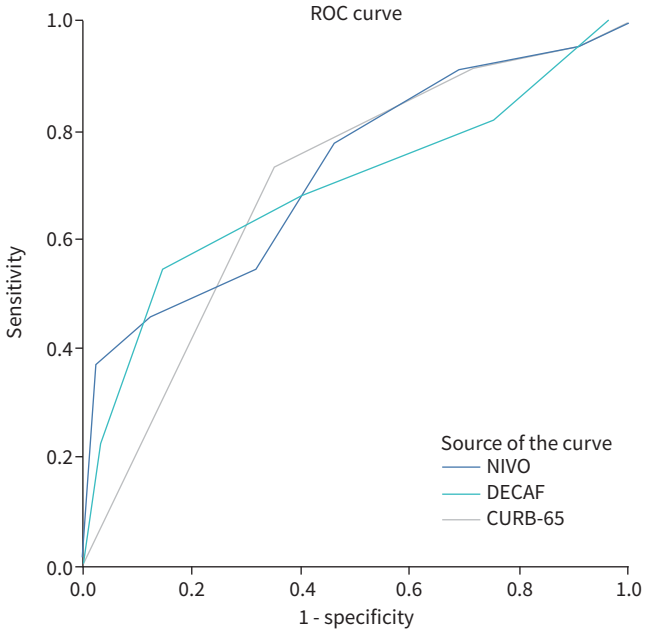


**FIGURE 1** Receiver operating characteristic (ROC) curve analysis of the noninvasive ventilation outcomes (NIVO) score and comparator tools (examining inpatient mortality) in clinical diagnosis patients. DECAF: dyspnoea, eosinopenia, consolidation, acidaemia and atrial fibrillation; CURB-65: confusion, urea >7 mmol·L$^{-1}$, respiratory rate ⩾30 breaths·min$^{-1}$, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years.

**TABLE 4** Comparisons of the noninvasive ventilation outcomes (NIVO) area under the receiver operating curve (AUROC) in clinical diagnosis patients

| Clinical score in clinical diagnosis patients | AUROC (95% CI) | AUROC difference from NIVO | p-value of difference[#] |
|---|---|---|---|
| **NIVO score** | 0.724 (0.598–0.851) | NA | NA |
| **CURB-65 score** | 0.695 (0.575–0.815) | 0.029 | 0.69 |
| **DECAF score** | 0.695 (0.554–0.836) | 0.029 | 0.54 |

Data are presented as AUROC with 95% CI. NA: not available; DECAF: dyspnoea, eosinopenia, consolidation, acidaemia and atrial fibrillation; CURB-65: confusion, urea >7 mmol·L$^{-1}$, respiratory rate ⩾30 breaths·min$^{-1}$, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years. [#]: compared using the method of DeLong.

patients. Additionally, the NIVO score has been incorporated into the British Thoracic Society "Respiratory Support Audit" and is hoped to be used to benchmark across different healthcare sites.

BMI and prevalence of acute confusion were higher in CD patients. The difference in BMI may in part be due to more severe COPD in the confirmed diagnosis group, and inclusion of patients with OHS in the CD group. Within the CD group, BMI tended to be higher in those with subsequent nonobstructive spirometry (table 5). Decompensated OHS requiring ventilation is often unrecognised and frequently misdiagnosed as AECOPD. [7] Compared with CDs with subsequently obstructive spirometry, those with confirmed COPD had poorer performance status (eMRCD) and lower $FEV_1$ (table 5) in keeping with more-severe underlying disease. The reason for the difference in confusion is not immediately clear; acidaemia, age, DECAF score [9] and consolidation were similar. Misdiagnosis of AECOPD, and thus inclusion of patients who did not have COPD, may explain the numerically lower AUROC of the NIVO score in CD patients compared with the NIVO validation study. It is important to note that the number of CD patients (n=111) was small and analysis is limited by being underpowered; further examination in such a population is required to confirm our findings; this may be feasible in the future with the national audit program, but this is a limitation of the current study.

Spirometry is required to confirm the diagnosis of COPD [8]. Disappointingly, of the 89 CD patients who survived to discharge, fewer than half had diagnostic spirometry performed in the subsequent year. In those that did, four out of five demonstrated airflow obstruction; such patients had significantly better $FEV_1$ and eMRCD scores than the confirmed COPD group, although they still had marked limitation. The reason(s) for later formal diagnosis of COPD in CD patients is not immediately clear and likely multifactorial, including patient factors (not presenting to medical attention) and healthcare factors (failure of recognition of the symptom complex of COPD or resource limitations). Overall, by 1 year, 63% of CD patients treated as AECOPD with ventilation for respiratory failure had not had a diagnosis of COPD

**TABLE 5** Spirometry, eMRCD and BMI in "confirmed COPD" and "clinical diagnosis" (CD) patients both with and without subsequent obstructive spirometry

| Measurement | Confirmed COPD (NIVO validation cohort) | CD: subsequent obstructive spirometry | CD: subsequent nonobstructive spirometry |
|---|---|---|---|
| Subjects, n | 733 | 33 | 8 |
| Days to spirometry | NA | 59±76 | 141±147 |
| $FEV_1$ (L) | 0.84±0.36[#] | 1.02±0.49[#] | 1.23±0.39 |
| FVC (L) | 1.96±0.71 | 2.15±0.76 | 1.63±0.55 |
| $FEV_1$/FVC ratio | 0.44±0.13 | 0.47±0.10 | 0.75±0.05 |
| $FEV_1$ % predicted | 37.2±15.4 | 41.5±14.4 | 61.3±20.8 |
| FVC % predicted | 67.4±21.9 | 70.0±19.7 | 69.8±25.0 |
| eMRCD, median (IQR) | 5a (4–5a)[¶] | 4 (3–4)[¶] | 4 (4–5a) |
| BMI | 25.5±8.0 | 26.7±7.1 | 30.5±8.9 |

Data are presented as mean±SD, unless stated otherwise. eMRCD: Extended Medical Research Council Dyspnoea Score; NIVO: noninvasive ventilation outcomes; NA: not available; $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; IQR: interquartile range; BMI: body mass index. [#]: $FEV_1$ CD with subsequent obstructive spirometry *versus* confirmed COPD (t-test) p=0.0060. [¶]: eMRCD CD with subsequent obstructive spirometry *versus* confirmed COPD (Mann–Whitney U-test) p⩽0.0001.

confirmed. However, these patients have suffered a life-threatening event, and among those who survive, symptom burden and the risk of readmission and death remain high. The low rates of spirometry are very concerning. Spirometry should be performed before discharge, with appropriate follow-up to ensure correct diagnosis and optimise management. Unfortunately, our results are unable to capture the effects or potential harm of unnecessary or ineffective treatments as a consequence of diagnostic inaccuracy.

The strengths of this real-world study include diversity within the population (including socioeconomic status and rurality), participating hospitals (district general hospitals to tertiary centres) and the capture of consecutive patients with broad inclusion criteria. Limitations include a reduced dataset when compared with the NIVO validation cohort and follow-up for CD patients with no differentiation between "new" or "existing" diagnoses. Interestingly 13.5% of CD patients were receiving long-term oxygen therapy. It may be that these patients did have historic spirometry, although we did not find this after comprehensive searches of current and old volumes of notes, electronic records, lung function databases and contacting patients' general practices.

One potential mechanism for improving diagnosis could be to perform inpatient spirometry in all patients admitted as "AECOPD" who have no previous spirometry available. While absolute $FEV_1$ changes around admission, the $FEV_1$/FVC ratio remains similar between admission and 2 months after discharge [12]. It may be that adopting this approach would help reduce misdiagnosis and is worthy of future research. Ruling out airway obstruction in some patients could reduce inappropriate treatment of OHS, among other conditions, with medications such as systemic corticosteroid and bronchodilators. Other methods of improving COPD diagnosis rates, such as targeted spirometry screening have been proven to be effective, but are not yet widely adopted [13]. Patients with AECOPD are at particularly high risk of readmission and death soon after discharge [14]. Even in those who did have confirmatory spirometry, the mean time to readmission or death was 2.5 months, after the highest risk period for readmission and the chance to influence this has passed. The performance of the NIVO score was good in the clinical diagnosis group, but some patients may have been misdiagnosed as having COPD; future studies examining the utility of the NIVO score in other conditions causing respiratory acidaemia, such as OHS, are warranted.

In conclusion, this study suggests that the NIVO score can be utilised in patients with a clinical diagnosis of AECOPD but who have not had previous diagnostic spirometry. This could improve shared decision-making and challenge prognostic pessimism in this group of patients. However, we have also highlighted shortcomings in diagnosis and follow-up after hospitalisation for AECOPD, even when patients have required ventilation for respiratory failure. In the UK COPD national audit, spirometry results were often unavailable. Spirometry performed in primary or secondary care should be immediately available to frontline clinicians [15]. Significant improvements in COPD diagnosis could be achieved in engaged patients through targeted case-finding prior to hospitalisation [13] and by performing pre-discharge spirometry in all patients admitted for presumed AECOPD, irrespective of exacerbation severity. Airflow obstruction should still be confirmed in the stable state, but the high agreement between spirometry in patients with an appropriate history and high risk of readmission and death among those surviving to discharge justifies this approach [12, 14].

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Ethics statement: Ethical approval was provided by the National Health Service (UK) Health Research Authority (approval number 16/NE/0213).

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