 

**The ROX index in the Emergency Department – predicting NIV failure: a prospective observational study**

Shortness of breath is a common presenting complaint to Australian Emergency Departments. One treatment for this patient group is non-invasive ventilation. This study hopes to discern the utility of the ROX index in predicting the failure of NIV.

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Background

Shortness of breath (SOB) is a common presenting complaint to an Emergency Department (ED). Whilst shortness of breath accounts for around 5% of annual Australian ED presentations, it accounts for around 11% of ward admissions, and 20% of admissions to intensive care units (ICU). These rates are increased in winter, with SOB accounting for up to 10% of ED presentations1. The most common cause of SOB in a patient presenting to ED is pneumonia (20%), followed by heart failure (14%) and exacerbations of chronic obstructive pulmonary disease (COPD)1. For some patients, treatment with non-invasive ventilation (NIV) is instigated; this established therapy provides continuous positive airway pressure to treat the underlying hypercapnia and hypoxia. Positive airway pressure is delivered either by a high-flow nasal cannulae (HFNC), or via a face mask device.

The failure rate of NIV is high, however, with studies demonstrating up to a 27% failure rate in patients where the dyspnoea is caused by exacerbation of COPD2, and up to 56% in dyspnoea caused by community acquired pneumonia3. One study demonstrated a failure rate of 47% across all causes of dyspnoea4. Failure is defined as any of worsening of the arterial pH, a decreasing arterial pO2, a rising arterial pCO2 or a decreasing level of consciousness, whilst on NIV. Where appropriate, the next step in treatment following NIV failure is tracheal intubation and mechanical ventilation, and subsequent ICU admission.

Given that some studies have shown that delays in providing mechanical ventilation can decrease survival in some SOB patients, early prediction of NIV failure offers clinicians an opportunity to provide more definitive care in a timely fashion, particularly in situations where patients are deteriorating, or not responding to treatment.

Previous studies have shown that patients commenced on NIV, regardless of the underlying disease process, with an arterial pH of less than 7.25, and a pCO2 of greater than 75, within 1-2 hours on NIV treatment have significantly increased rates of NIV failure (Odds Ratio 9.3)5. Equally, one study demonstrated a higher likelihood of NIV failure regardless of the underlying pathology when the patient scored highly on a newly developed prediction marker, the HARCOR score4. This study calculated a score combining measures of heart rate, acidosis, conscious level, oxygenation and respiratory rate, which if increasing, increased the likelihood of NIV failure by an odds ratio of 1.73 for every point raised.

Other studies have focused exclusively on NIV use in patients with specific underlying pathologies. In one study exclusively concerning COPD patients, NIV failure was associated with higher serum urea, lower arterial pH and higher arterial pCO2 pre-NIV therapy, as well as a failure to improve the pH within one hour of NIV treatment6. Other studies demonstrate an increased NIV failure rate the longer the duration of symptoms pre-NIV treatment2, or an increase in failure if NIV was used previously in the prior 12 months7.

Concerning studies predicting NIV failure in patients suffering acute pneumonia, one study demonstrated a higher failure rate if a patient had a raised simplified acute physiology score, and a lower arterial pH3. Equally, a second study demonstrated the presence of pneumonia alone as being predictive of NIV failure8.

However, there are few studies which afford clinicians a real-time method by which to predict NIV failure regardless of the underlying disease process.

Recently, a study investigating pneumonia patients demonstrated the potential to utilise a newly devised prediction criterion, the ROX index9. This study concerned patients with acute respiratory failure, caused by pneumonia, treated with high-flow nasal cannulae for 12 hours or more. After 12 hours, a calculation was made of the ratio of the patients’ saturations divided by the inspired oxygen concentration, to the respiratory rate (SPO2/FIO2 to RR). Investigators found that a ROX index greater than or equal to 4.88 at 12 hours after HFNC onset successfully predicted treatment success (Sensitivity 70.1%, Specificity 72.4%, Positive Predictive Value 89.4%, Negative Predictive Value 42%, Positive Likelihood Ratio 2.54, Negative Likelihood Ratio 0.41).

**Objectives**

Primary objective

To assess the utility of a pre-NIV ROX score as a useful predictor of NIV failure in all breathless patients commenced on NIV in the ED. Failure is defined as the progression to intubation.

Secondary objectives

To perform a subgroup analysis of NIV-ROX index accuracy based on underlying pathology.

To develop a near-real time scoring system that can be used to generate NIV ROX curves for early warning of failure or to identify the possibility of weaning.

Hypothesis

The ROX index is predictive of patients who are likely to fail non-invasive ventilation.

Secondary hypothesis

The delta ROX index is predictive of NIV failure or possibility of weaning.

Study design

A prospective observational study of all patients commenced on NIV in ED, regardless of their underlying pathology.

Location

Liverpool Hospital, Sydney NSW

Royal North Shore Hospital, NSW

Campbelltown Hospital, NSW

Royal Prince Alfred Hospital, NSW

Study duration

A one-month prospective audit of patients within our inclusion criteria will occur at Liverpool Hospital and two other sites in order to gather an indication of the total number of patients available to be included in the study. A power calculation, described below, will estimate the number of patients to be recruited, in order for any difference between NIV failure and non-failure groups, and any regression analysis, to reach statistical significance.

Study population and recruitment

This pragmatic study will include all patients aged 18 or over who are commenced on NIV for breathlessness in the ED, as judged by the treating clinician, regardless of predicted underlying pathology. Breathlessness will be defined by the treating clinician, who will routinely use subjective markers of a patient’s work of breathing as part of clinical assessment, combined with objective data on gas exchange.

**Exclusion criteria**

* Prior advanced care directive specifying ’not for intubation’
* Comorbidities & disease severity where clinician/family provide limitations of care (i.e. not for intubation or ICU)
* NIV utilised as a pre-oxygenation strategy with intention to intubate
* Patients electively intubated for diagnostic or therapeutic procedures, such as fibreoptic bronchoscopy and surgery

**Data collection**

The following data will be collected from the electronic medical records, and entered into the REDCap software system:

* Patient demographics
  + Age
  + Sex
    - Male
    - Female
* Comorbidities
  + Immunosuppression
  + Chronic heart failure
  + Chronic liver disease
  + Chronic respiratory disease
  + Chronic renal failure
* Triage date and time
* Triage (or first recorded) observations
  + Alertness as per AVPU scale
  + Heart rate
  + Respiratory rate
  + Oxygen saturations
  + Temperature
  + Blood pressure
  + BSL
  + Work of breathing (as judged by bedside clinician)
* Time commenced on NIV
* Observations at NIV T = 0
  + Alertness as per AVPU scale
  + Heart rate
  + Respiratory rate
  + Oxygen saturations
  + Temperature
  + Blood pressure
  + BSL
  + Work of breathing (as judged by bedside clinician)
* Initial NIV settings
  + See table 1
* ROX index at time of NIV initiation
* Initial CXR findings
  + Number of affected quadrants
* Initial Blood gases
  + Arterial/Venous
  + FiO2
  + pH
  + pO2
  + pCO2
  + HCO3
  + BE
  + Lactate
  + Calculated A-a gradient & P/F ratio (if arterial)
* Serial blood gases at 6, 12 hours (if available)
  + As above.
* Working diagnosis as recorded in patient notes by treating clinician
  + Pneumonia
  + Asthma
  + COPD
  + Congestive cardiac failure
  + Viral pneumonitis
  + Pulmonary embolism
  + Other
* Serial observations (paired with NIV settings) minimum four hourly
  + Alertness as per the AVPU scale
  + Heart rate
  + Respiratory rate
  + Oxygen saturations
  + Temperature
  + Blood pressure
  + BSL
  + Work of breathing (as judged by bedside clinician)
* Serial NIV settings, including any changes minimum four hourly
  + See table one
* Disposition
  + Admitted ICU/HDU
  + Admitted ward
  + Died in ED
  + Discharged home
* Clinical course
  + Intubated
    - Time of decision to intubate
  + Not intubated
    - NIV success
    - Died in hospital
* Hospital LOS
* APACHE II of 12h ICU admission
* SOFA ICU admission
* Final diagnosis once treatment completed
* 30-day mortality

**Informed consent, Confidentiality and Privacy**

Gaining informed consent in the ED setting has been the subject of much debate, and in the circumstances of retrospective research using data only, the risk to the individual patient is extremely low, and essentially translates to those risks surrounding privacy principles. The NHMRC National Statement (section 2.3.6 (a)) requires that the research ‘carries no more than low risk’ and that the ‘only foreseeable risk is one of discomfort’10.

There are other risks inherent in seeking informed consent from vulnerable ED patients, including the risk of creating additional threats to privacy by having to link information to locate and contact individuals to seek their consent. There are risks of inflicting psychological, social or other harm by contacting individuals with conditions in certain circumstances, and there are considerations of difficulty of contacting individuals directly when there is no existing or continual relationship between the organisation and the individuals.

Alternatives to prospective informed consent include proxy consent, a waiver from individual participant consent and retrospective or deferred consent. There is evidence in proxy consent that the proxy may demonstrate poor agreement with the wishes of the participant; also, proxy consent may not be available in the timely manner necessary for interventions with a narrow therapeutic window. Deferred consent is used when it is not possible to obtain prospective informed consent from the participant or proxy, and consent is obtained from the participant as soon as is feasible after the intervention. However, not only does deferred consent run the risk of loss to follow up of patients enrolled in the study, but particularly in the emergency setting also involves attempts to contact the patient after discharge, a process which may cause unnecessary psychological distress and anxiety. A waiver of individual consent has been suggested as a solution to many 'low-risk' investigations in emergency medicine, allowing consideration of factors such as minimal or no risk to the patient or staff, and the mandate to produce sound research-based evidence for time-critical interventions.

A waiver of consent is sought and is done so in relation to the National Statement on Ethical Conduct in Human Research: Chapter 2.3: Qualifying or waiving conditions for consent. A waiver of participant consent is sought as this study is non-invasive in that it uses demographic, physiological and patient stay data which are measured routinely as part of clinical care, and subsequently analyses the predictive power of these data in relation to documented outcomes. These data will not be changed or used in any other way than for the purpose of this study, and no other data on the recruited patients will be collected in addition to that used in routine patient assessment and management. Identifiers will be used to collect data on demographics, investigations and outcomes; once these data are linked to the clinical data collected as part of routine ED and ICU assessment and management, the patients will be de-identified and data stored with patients allocated a unique study number. The ability to re-identify patients from these data will then not exist.

There is no risk to the rights, privacy or professional reputation of carers, health professionals and/or institutions as the study solely concerns the impact of a single clinical intervention which is used ubiquitously and has no intent to identify individual clinicians or carers, nor to use the data as commentary on the institutions concerned.

**Data analysis**

The primary outcome (dependent variable) is endotracheal intubation and commencement of mechanical ventilation. Patients for whom futility of active respiratory support is recognised will be reported but excluded from further analysis.

The predictive capacity of study variables in relation to the primary outcome will be assessed by receiver operating characteristics (ROC) with the ROX index being the a priori predictive variable. The area under the curve (AUROC) and its 95% confidence interval will be reported together with the Youden index for the optimal combination of sensitivity and specificity to predict the primary outcome. Cut-off values for pre-set sensitivities and specificities of 80% and 80% will be used to reflect the degree to which clinicians might accept under- and over-estimation of the predictive capacity of the candidate variable. Variables with a P value <0.2 on ROC analysis will be considered candidates for further statistical evaluation in a binary logistic regression analysis against the dependent variable. The goodness of the fit of the model will be reported by the Hosmer-Lemeshow test and the odds ratios and 95% confidence intervals for any independent variables will be reported. The association between the ROX index and any other independent predictors identified in the logistic regression will be further assessed by Cox proportional hazards modelling with adjustment for the candidate independent variables and reported by the hazard ratio and the 95% confidence interval.

The overall performance of the ROX index versus the performance of the logistic regression model will be compared according to DeLong et al11 for the standard errors of the areas under the curves.

Physiologically or clinically impossible values will be treated as missing. No imputations will be performed for missing data. The degree of missing data will be reported with the model based on the most complete dataset possible. Sensitivity analyses for best-case and worse-case scenarios will be reported12.

It is estimated based on previous literature that failure of NIV failure leading to intubation will be observed in 30% of patients. Ten events, i.e. intubations, are assumed to be needed per candidate variable and a comprehensive regression model encompassing up to six candidate variables (twice the number included in the ROX index) would hence need 90 events, equal to 180 patients. With a study attrition rate of 10% to account for futility and patients with missed inclusion, the sample size is estimated to be 200 patients13.

All statistical analyses will be performed using the latest version of the SPSS statistical software and will be independently analysed by the data scientist employed within the South Western Emergency Research Institute (SWERI).

**Data storage and record retention plan**

Data will be stored in the Principal Investigator's office, in the Emergency Department,

Liverpool Hospital. Once case and patient data are identified and linked, a unique linkage key

will be generated for each set of linked data, and identifiers removed. Information will be

stored in electronic form (REDCap database, Vanderbilt University). REDCap (Research

Electronic Data Capture) is a secure, browser-based, metadata-driven, electronic data capture software designed by Vanderbilt University. The licensing for REDCap for this study is via the South Western Sydney Clinical School of the University of New South Wales, with data stored behind a firewall.

This database will be stored on the Principal Investigator's computer and will not be shared or distributed in any way, other than to the project investigators. As stated above, a unique

linkage key will be generated for each set of linked data, each comprising records from the

Emergency Department Information System, physiological and pathology data from ED and

hospital records, and outcome data from inpatient clinical notes and Hospital Information

System. Once linkage is achieved between the data, all identifying details will be removed.

From this point all analyses will be carried out on the de-identified dataset, and access to the

prior identified data will only be available to the Principal Investigator for the purposes of

security; i.e. if loss of de-identified data occurred due to computer malfunction, the database

should be able to be rebuilt based on the original information. Once the de-identified database is complete, all identifiable data stored within the project database will be erased. This will, of course, not affect the original patient records and health information, which are stored in the standard fashion.

This information will be stored for 5 years, in keeping with the NHMRC Australian Code for

the Responsible Conduct of Research Practice, Section 2. Magnetic media will be erased before being discarded, and all data will be removed from the drives to the new system. The most secure method to prevent the accidental disclosure of information will be used by reformatting the hard disc.

**Outcomes and significance**

There will be no direct benefit for the direct participants in this study. This is because although the study is prospective in nature, retrospective use is being made of patient physiology and therapeutic data and will therefore be unrelated to patient management or treatment. This study looks at investigating a predictive model based on patient data, which will not be used for any patient-related purposes within the study.

There is potentially a substantial benefit for the institution, as it will add considerable knowledge about the patients attending Liverpool ED with a range of acute and critical respiratory illnesses and undergoing urgent treatment, and will thus inform the medical and nursing processes provided for these patients.

**Timeline**

We aim to adhere to the following timeline:

Protocol completed: March 2019

Ethics approval: March 2019

Study commencement: November 2019

Recruitment completed: Mid 2020

Data analysis: Late 2020

Study write up: Late 2020

Study published: Early 2021

**Budget**

There is no staffing budget associated with this study. Clinicians involved will undertake the research in their own time.

It is hoped that a grant may help fund some data gathering hardware, which will be attached to our NIV machines in the associated Emergency Departments in order to capture, live, the necessary data onto RedCap:

* 32 iPads – total cost $19,168

**Outcome and significance**

We hope that this study will identify the ROX index as a useful predictive tool to help future clinicians anticipate NIV failure. Based on this predicted clinical course, clinicians may be able to better direct the patient’s therapy, for example identifying the need for mechanical ventilation earlier in the clinical course, thus affording the patient earlier more definitive treatment.

**Publication policy**

Following completion of this study, we hope to share our findings at a local, national and international level through academic conferences and peer-reviewed journals.

**Appendix**

**Table 1**

|  |  |
| --- | --- |
| Mode | * Continuous positive airway pressure (CPAP) * Bi-level positive airway pressure (BIPAP) |
| Concentration of oxygen delivered | * Fraction of inspired oxygen (FiO2) |
| Settings | * Continuous positive airway pressure (CPAP, cmH2O)) * Positive end expiratory pressure (PEEP, cmH2O) * Inspiratory positive airway pressure (IPAP, absolute cmH20) * Pressure support (absolute cmH20) |

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