COPD: Comparison of existing prognostic tools for 1 year mortality and assessment of symptom burden to facilitate Advance Care Planning

Scientific Abstract:

**Background:** Following hospitalisation for an exacerbation of COPD (ECOPD), one year mortality is 23.2%. Compared to inoperable lung cancer, patients with severe COPD have a greater symptom burden but much lower access to palliative care and advance care planning. Improved prognostication will support selection for, and use of, these services.

**Aims:** To facilitate palliative care and advance care planning in patients surviving hospitalisation for ECOPD, we will: 1) compare the performance of prognostic tools for prediction of one year mortality; 2) assess ease of completion of these tools; 3) assess symptom burden and quality of life over one year.

**Methods:** In patients with ECOPD surviving to hospital discharge, established prognostic tools and a novel tool (from the PEARL derivation cohort n=824) will be compared for prediction of one year mortality: a) within the existing PEARL validation cohort of 1,593 patients, and b) prospectively in at least 310 patients. Patients will undergo longitudinal assessment of symptom burden and quality of life.

**Benefits:** This study will identify which prognostic tool performs best for one year mortality outcome in patients hospitalised with ECOPD. This should lead to more frequent and appropriate engagement with palliative care and advance care planning, and prompt timely discussions with patients about end of life planning.

Lay Summary:

Chronic Obstructive Pulmonary Disease (COPD) is a common progressive lung disease which causes breathlessness and frequent exacerbations. During exacerbations patients become more breathless, often requiring hospitalisation. Patients with severe COPD commonly become housebound, lose their independence and suffer significant depression and anxiety. Hospital admissions become increasingly common towards end-of-life; however this also means that hospitalisation is a good opportunity to identify patients at risk of poor outcome. Such patients, when well-informed, may wish to consider alternatives to admission and avoidance of intrusive procedures and treatments. Unfortunately, predicting which patients are likely to die in the near future is particularly challenging in non-malignant disease. Patients with severe COPD have a higher symptom burden than those with incurable lung cancer, yet they are less likely to receive specialist palliative care, or to have engaged in advance care planning (where patients discuss and document their wishes regarding their future care). To improve provision of palliative care services and ensure patients are given the opportunity to make truly informed decisions about their future care, the first step required is accurate identification of those who would benefit.

Well-designed prognostic tools outperform clinician judgement in most settings. We will compare the accuracy of one year mortality prediction, and ease of completion, of several clinical tools in patients who survive an ECOPD requiring admission. This will initially be performed using data collected during previous research (we developed a number of tools now routinely used), then prospectively confirmed in a minimum of 310 patients admitted consecutively with an ECOPD. The latter group of patients will be invited to participate in a follow-up study, assessing symptom burden, quality of life, and readmissions.

We anticipate that this project will improve access to palliative care, and help to facilitate well-informed discussions with patients and their families about their future care. This may include whether they would like to be readmitted to hospital or cared for at home, and which offered interventions they would be willing to accept in hospital. This should ensure better symptom control
and quality of life for patients with severe COPD reaching the end of their life, and empower them to avoid aggressive interventions if preferred. This is all a routine part of care for patients with terminal cancer but is currently often not afforded to patients with non-cancer conditions.

Background:
Exacerbation of COPD (ECOPD) is the second commonest reason for emergency hospital admission in the UK.\(^1\) National audits between 2008 and 2014 show a substantial rise in 90-day readmissions (from 33% to 43%).\(^2\) Among those who survive, 23.2% die within 1 year.\(^3\)
In severe COPD, there is a huge unmet need for appropriate palliative care and advance care planning. Compared to unresectable lung cancer, quality of life (QOL) is worse,\(^4\) and levels of disability, anxiety and depression greater.\(^4\) In addition to high symptom burden,\(^4\) frequent hospital admissions and invasive interventions at the end of life are common.\(^4\)\(^-\)\(^10\) Despite this, advance care planning is rarely addressed, largely reflecting the uncertainty of prognosis in COPD; in malignancy deterioration is more predictable, and engagement with advance care planning and palliative care services is the norm.\(^4\)\(^,\)\(^6\)\(^-\)\(^12\) This uncertainty can lead to reluctance from clinicians to involve palliative care services, or to have frank discussions with COPD patients about their future care, to the detriment of their QOL.\(^13\)\(^-\)\(^15\) Among those patients surviving to discharge, disease-specific risk stratification tools have been developed for readmission and death,\(^3\)\(^,\)\(^16\)\(^-\)\(^19\) whilst other non-COPD specific tools may be applicable in this setting.\(^20\)\(^,\)\(^21\)
Due to time pressures during hospitalisation,\(^22\) the provision of acute care takes precedence over anticipatory planning. Acute, general and respiratory physicians must feel empowered to, and capable of, incorporating palliative care and advance care planning into their own practice,\(^8\)\(^,\)\(^12\) and a simple prognostic tool should assist with this. Integrating these aspects of care into routine COPD management would be supported by patients.\(^6\)\(^,\)\(^8\)\(^,\)\(^23\)\(^,\)\(^24\)

Aims:
1. Determine which clinical tool is most appropriate to identify patients at risk of death within one year, in terms of performance and ease of completion, following hospitalisation with ECOPD.
2. Patients surviving beyond one year may have palliative care needs. We will assess quality of life, symptom burden and utilisation of healthcare services in this patient group over one year, and compare to risk groups within the prognostic tool.

There is a pressing need to more accurately identify which patients with ECOPD surviving to discharge are most at risk of adverse outcome, and likely to benefit from advance care planning and palliative care. The findings will be presented nationally and published in an international journal. The project is supervised by two consultant respiratory physicians and a consultant in palliative medicine, and will be primarily conducted by a respiratory palliative care fellow.

Methods:
Comparison of prognostic tools:
The PEARL score predicts readmission or death within 90 days of discharge following ECOPD, and was developed by the lead supervisor's research team.\(^3\) Within the PEARL derivation cohort (2 hospitals, 824 patients), they have developed a novel tool to predict one year survival. The performance of this novel tool and existing COPD prognostic tools (BODEX,\(^17\) PEARL,\(^3\) COPD PIG,\(^20\) CODEX,\(^16\) ADO,\(^12\) DOSE,\(^18\) the non COPD specific SPICT\(^21\) and the new BARC\(^25\)) will be compared in the PEARL validation cohort (6 hospitals, 1,593 patients).
Performance of all tools will also be further prospectively assessed in a minimum of 310 patients across two sites. The COPD-PIG is intended to only be scored in patients who the clinician “would not be surprised” if they died within one year; the performance of this tool cannot be fully assessed
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retrospectively. Prospective validation will also allow an assessment of the ease of data collection; this is not available for the existing PEARL cohort but is a key consideration in selection of the final tool to ensure it is appropriate for widespread use on hospital wards. Consecutive, unique patients admitted to Northumbria Healthcare NHS Foundation Trust and Newcastle Upon Tyne Hospitals NHS Foundation Trust with ECOPD will be identified. Demographic and clinical indices, including the components of the nine prognostic tools, will be collected. Caldicott and Research and Ethics Committee approval are in place. Hospital readmissions, utilisation of other healthcare services such as the local palliative care teams and Hospice and survival will be assessed over one year. In common with similar studies, this validation study will be non-consenting.

Patients identified as high-risk by the selected tool who survive beyond one year may still warrant palliative care input if their symptom burden is high. The patients enrolled in the validation study will be invited to participate in a consenting longitudinal outcomes study, aiming for at least 50% participation. Symptom burden and functional status will be assessed using the St George’s Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Score (HADS), Australian modified Karnofsky Score (AKPS), eMRCD score, and modified Borg scale at baseline, and 1, 3, 6 and 12 months. The intention is for the baseline and 3 month assessments to be conducted via face to face meetings, and the additional 1, 6 and 12 month assessments to be conducted over the phone; however, in order to maximise the number of participants we will be flexible with home/hospital visits versus telephone interviews according to patient preference. This data will be used both to calculate the relationship between symptom burden and death, and to identify the characteristics of patients who are especially symptomatic.

Inclusion and Exclusion Criteria:
All patients consecutively admitted with ECOPD will be screened.

Inclusion Criteria:
1. Age 35 years or older.
2. Smoking history greater than or equal to 10 pack years.
3. Obstructive spirometry (FEV1/FVC < 0.7).
4. ECOPD primary diagnosis.
5. Survival to discharge.

Exclusion Criteria:
1. Previous inclusion in the study.
2. Malignant neoplasm or other pathology likely to limit survival to less than 1 year.
3. For the longitudinal study only, inability to give informed consent.

Statistical analysis:
The primary outcome of interest is prediction of one year mortality. Assuming a one year mortality rate of 23.2%, an area under the receiver operating characteristic (AUROC) curve of 0.70, with a standard error for the AUROC curve of 4%, a minimum sample size of 310 subjects is required (validation cohort).

The characteristics of the cohort will be summarised using standard descriptive statistics appropriate to the level and distribution of the data. Groups will be compared (including by mortality outcome) using standard tests of statistical inference (e.g. t-test, Mann-Whitney U test, Fishers exact test). The performance of candidate prognostic tools will be compared by 1) assessing the positive and negative predictive value within the high-risk groups; and 2) AUROC curve analysis, with performance compared using the method of DeLong et al. Where data imputation is required, this will be done using multiple imputation methods. Statistical significance will be set at 5% throughout. The statistical analysis plan will be finalised prior to end of recruitment to avoid potential bias.
Outcome Measures:

Validation Study:
Primary outcome:
Positive predictive value and sensitivity of the prognostic tools listed for prediction of one year mortality.*

Secondary Outcomes:
1. Ease of completion of prognostic tools assessed by: a) Likert scale; b) missing data.
2. Area under the receiver operating characteristic curve for each prognostic tool.
3. Negative predictive value of the prognostic tools for prediction of one year mortality.
4. Hospital readmission rates at 30, 90 and 365 days.
5. Proportion of patients on the palliative care register and relation to mortality.
6. Utilisation of palliative care services: hospice; community palliative care team.
7. Inter-observer agreement on scoring.

*This is an exploratory study. The optimal tool to identify patients for advance care planning needs to offer high PPV (i.e. the substantial majority of those identified at high risk of dying should not survive beyond one year) and reasonably high sensitivity (i.e. most deaths within one year should be identified). Ease of completion must also be considered as this will strongly influence engagement.

Longitudinal cohort:
In the whole cohort and individual risk groups within the prognostic tools, assess:
1. Baseline SGRQ, HADS, modified BORG, AKPS.
2. Mean change in SGRQ, HADS, modified BORG, AKPS compared to MCID.
3. Duration SGRQ, HADS, modified BORG, AKPS maintained above baseline.
4. Relation between clinically significant anxiety and depression on discharge and survival, QoL, functional status and readmissions.
5. Best prognostic tool to predict poor QoL and/or death within one year, as per positive predictive value and sensitivity.

Patients in a high mortality risk group identified for advance care planning who do not die are not “false positives” if they have a high symptom burden. The proportion of patients with high symptom burden not identified is also clinically relevant.

Ethical Considerations:
To validate a meaningful predictive tool it is essential that patients at the extremes of mortality risk are not selectively excluded. The most unwell patients would be unlikely to be able to consent, introducing a significant selection bias were they to be excluded. In common with previous prognostic tools developed by this group and others, the validation study will not require individual patient consent. All included indices are routinely available and participation will not influence normal clinical care. Mortality and readmission data is tracked electronically in all patients. All records will be anonymised.

All patients surviving to discharge will be invited to partake in a follow up study assessing patient reported QOL. Participation in this part of the study will require written informed patient consent. IRAS approval is in place for the existing cohort (REC: 08/H0905/88 & 12/NE/0379) and for the prospective validation and longitudinal cohorts (REC: 18/NE/0226).

Data Handling:
Caldicott and Research and Ethics Committee approval are in place (REC: 18/NE/0226). Patients in all arms of the study will be identified by the usual care team. Patients must be identifiable to follow up
data queries or insert readmission data. Clinical data will be kept on a password protected server, on a secure database with no patient identifiable information; a separate secure database will contain patients’ identifiable information but no clinical details, with ID codes to link patients to their clinical data. Patients’ notes will only be reviewed in usual clinical areas or the office of the research fellow. Case Report Forms will be kept in a locked filing cabinet in a locked office accessible by research staff only. Access to patient identifying information will be via trust servers only. Staff will all be NHS employees.

Research Timetable and Management:
Ethical approval is in place (REC: 18/NE/0226). Data collection for the prospective cohort is expected to begin in January 2019. As the prospective prognostic study will be non-consenting, recruiting 310 patients is expected to be fully achieved by summer 2019.
Prof Stephen Bourke will act as chief investigator. He, Dr Katie Frew and Dr Carlos Echevarria will co-supervise the Respiratory Palliative Care Fellow Dr Sarah Gillespie. William Keith Gray undertook the power calculation and will provide on-going statistical support. Financial management, study sponsorship and data monitoring will be provided by Northumbria Healthcare NHS Foundation Trust Medicine department for the first year and Education department for the continuation of the project.

Benefits:
This study will identify which prognostic tool is most appropriate for use in patients hospitalised with ECOPD for 1 year mortality outcome, balancing performance with ease of completion.
Reliable prognostication in ECOPD, based on objective criteria should lead to more frequent and appropriate engagement with palliative care and advance care planning. Timely discussions about end of life planning will be facilitated. Patients will ultimately benefit from informed discussions about their future care, and avoiding future hospital admission when no longer appropriate to their condition and wishes. Such practice is commonplace in incurable cancer, but hitherto often denied to patients with end stage COPD, to their detriment.[4, 6]

Dissemination of results:
The findings will be disseminated to a broad regional, national and international audience, including respiratory specialists, general physicians and palliative medicine physicians, through presentations at local, national and international conferences, and publication in high ranking, peer-reviewed, journals.
Locally, we will keep patients, carers, primary and secondary care clinicians, healthcare managers, commissioners and neighbouring healthcare providers informed by publications in existing newsletters and presentations at local and regional meetings, conducted within both NHS organisations and the University.
The Chief Investigator (CI) is Chair of the British Thoracic Society COPD Speciality Advisory Group (SAG), which will aid dissemination of the results.
This is part of a very successful COPD research programme led by the CI, which includes development of the DECAF and PEARL prognostic scores,[3, 26, 27] with several publications in Thorax and two international prizes recognising the importance and impact of this work.[33, 35-37] The latest UK National COPD Audit report recommends that DECAF should be scored in all patients admitted with ECOPD.[2] We will be aiming for similar success in the dissemination and clinical implementation of the results of the proposed study.
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Research Team:
Prof Stephen Bourke, MBBC (hons), PhD, FRCP. Consultant Respiratory Physician and Professor of Respiratory Medicine.

Contact: North Tyneside General Hospital, Rake Lane, North Shields, Tyne and Wear, NE29 8NH. Stephen.bourke@nhct.nhs.uk
Role: Chief investigator, trial design and supervision, data analysis and interpretation.
Relevant Expertise: Conception, design and delivery of the programme of research leading to development of the “DECAF” prognostic score, including derivation, external and internal validation and on-going implementation studies. The latest National UK COPD Audit Report (Who Cares Matters; Feb 2015) recommends that the DECAF score should be performed in all patients admitted with AECOPD to inform clinical management. He was also CI on the PEARL derivation and validation study, developing the PEARL tool for 90 day mortality and readmission following admission with ECOPD. Stephen is currently Chair of the British Thoracic Society COPD Speciality Advisory Group.

Dr Katie Frew, MBChB, MRCP, PhD. Consultant in Palliative Medicine
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Role: Co-investigator, input into trial design and supervision, data analysis and interpretation.
Relevant Expertise: During her PhD studies, Katie conducted qualitative research into the use of sedation in palliative care. She currently leads Northumbria NHS Trusts’ hospital palliative care team, providing palliative care to all appropriate inpatients regardless of underlying diagnosis.

Dr Carlos Echevarria, MBBS, MRCP, PGDip, PhD. Consultant Respiratory Physician
Contact: Dept of Respiratory Medicine, Level 6, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Road, Newcastle Upon Tyne, NE1 4LP. Carlos.echevarria@nuth.nhs.uk
Role: Co-investigator, input into trial design and supervision, data analysis and interpretation.
Relevant Expertise: Carlos was the principal investigator in the DECAF validation and PEARL studies during his PhD, and as such has an in-depth understanding of the issues involved in this project.

Dr Sarah Gillespie, BMSc (Hons), MBChB, MRCP. Respiratory Palliative Care Fellow
Contact: North Tyneside General Hospital, Rake Lane North Shields, Tyne and Wear, NE29 8NH. Sarah.gillespie@nhct.nhs.uk
Role: PI on the study, data collection, data analysis and interpretation
Relevant Expertise: Sarah is a junior doctor with 14 months pre-specialist respiratory and 4 months pre-specialist palliative care experience, who intends to pursue a career in palliative medicine. She strongly feels that palliative care should be available to all who need it and is delivering this research to help further the evidence base in this area.

References: