**Title**: **Australia-modified Karnofsky Performance scale as an indicator of physical activity in people with COPD and lung cancer: an exploratory pooled data analysis**

**Authors**

Barbetta, Carlo.[1] MD, Allgar, Victoria.[2] PhD, Maddocks, Matthew.[3] PhD, Ribeiro, Catarina.[3] MSc, Wilcock, Andrew.[4] DM, Currow, David C.[5,6] PhD, Phillips, Jane.[5] PhD, Johnson, Miriam J.[6] MD, MBChB(hons)

[1] Respiratory Department, Ospedale Santa Maria degli Angeli, Pordenone, Italy

[2] Hull York Medical School, University of York, York, United Kingdom

[3]Cicely Saunders Institute, King's College London, London, United Kingdom;

[4]Department of Palliative Medicine, University of Nottingham, Nottingham, United Kingdom;

[5]IMPACCT, Faculty of Health, University of Technology Sydney, Sydney, Australia ;

[6]Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, United Kingdom.

**Corresponding Author:** MJ Johnson**,** Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, United Kingdom. Email: miriam.johnson@hyms.ac.uk; Tel: +44 (0)1482 463309

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**ABSTRACT**

**Objectives:** Patient-relevant measures of functional status are required in chronic obstructive pulmonary disease (COPD) and lung cancer in clinical practice and research. We explored the relationship between the Australia-modified Karnofsky Performance Status (AKPS) and measures of functional capacity and physical activity in these patient groups.

**Methods:** Pooled clinical trial data were analysed to explore the relationship between AKPS and: average daily steps [ADS], 6-minute walk distance [6MWD] and BODE score (COPD group). Receiver Operator Characteristic curves were produced to compare sensitivity and specificity of cut-offs (no dependency >70; high dependency <60) and area under the curve (AUC).

**Results:** Seven clinical trials included people with COPD (n=79) and lung cancer (n=150). To detect an AKPS >70, the optimal ADS cut-points were COPD, 3342 steps (AUC; 0.88, 95% CI: 0.79, 0.97; sensitivity 82%; specificity 76%) and lung cancer, 3380 steps (AUC 0.72, 95% CI: 0.64-0.81; sensitivity 61%; specificity 74%), and for 6MWD (COPD only) 242m (AUC 0.72, 95% CI 0.63, 0.81; sensitivity 73%; specificity 34%).

**Conclusions:** An AKPS score is strongly related to ADS in people with COPD and lung cancer. The AKPS may be useful in clinical practice and research to indicate levels of physical activity where ADS and 6MWT are not possible. Longitudinal data are needed to confirm these findings.

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**Keywords:** physical activity, chronic obstructive pulmonary disease, Lung Cancer, performance status, outcome measurement, functional independence

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and lung cancer are leading causes of morbidity, mortality and resource use worldwide. There are international calls for systematic research to improve symptom management, especially for chronic breathlessness.[1] Outcome measures must matter to patients, be minimally burdensome and reflect meaningful gain, especially for those with advanced disease.

The Six Minute Walk Distance (6MWD) is widely used in COPD to evaluate functional exercise capacity and forms part of the Body-mass index, airflow Obstruction, breathlessness (Dyspnea), and Exercise (BODE) disease severity score. Daily physical activity measured by accelerometry (Average Daily Step count [ADS]) is a patient-centred outcome which may correlate better with "real-life" activity.[2] However, people with advanced disease may be unable to complete a 6 minute walk test (6MWT), or use an accelerometer. In addition, accelerometers may not be available in routine clinical practice.

The Australia-modified Karnofsky Performance Scale (AKPS; online supplement Box 1) is a simple, validated measure, useful in advanced disease [3] and can be used across a range of settings. AKPS predicts survival and can reflect longitudinal changes. Although survival may be unaltered by a palliative intervention, improvements and/or maintenance in AKPS may allow independent living for longer; a highly patient-relevant outcome.

We investigated the relationship between AKPS and ADS, 6MWD, body mass index (BMI), forced expiratory volume in 1 second ($FEV_1$) and the modified Medical Research Council breathlessness score (mMRC) in people with advanced disease. We also assessed which was most useful in predicting functional independence.

## METHODS

This exploratory, individual pooled data, cross-sectional analysis used baseline data from seven palliative care clinical studies (see Online Supplement Table 1).[4-10]

In participants with COPD, the variables of interest were the AKPS, ADS, 6MWD, mMRC and BODE score (calculated from FEV1, mMRC, BMI and 6MWD data). In participants with lung cancer, the variables of interest were AKPS, ADS and 6MWD.

Ethical considerations

National Health Service ethical permission was not required for analysis of pooled anonymised data. (http://www.hra.nhs.uk/documents/2013/09/does-my-project-require-rec-review.pdf) Appropriate ethics approval and consent had been obtained for each contributing study.

Statistical analysis

Descriptive statistics present the participant population and performance status scores observed. Spearman correlations were used to measure the strength of the relationship between AKPS and the measures of physical activity, performance status and breathlessness. Receiver Operator Characteristic (ROC) curves were used to plot the sensitivity versus 1-specificity across varying cut-offs. A cut point of >70 (80 = normal activity with effort; some signs or symptoms of disease) for AKPS was chosen as this is the level below which a patient's daily independence is compromised. This was repeated using a cut point of < 60 (50 = considerable assistance and frequent medical care required) as this represents a large degree of care dependency.[3] The Area Under the Curve (AUC) with standard error and 95% confidence intervals (CI) were calculated. In determining optimal cut off values, the Youden index uses the maximum of vertical distance of ROC curve from the point (x, y) on diagonal line (chance line) which gives equal weight to sensitivity and specificity with no ethical, cost and prevalence constraints.[11]

All analyses were conducted with STATA SE (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## RESULTS

Online Supplement Tables 1 and 2 summarize the study population (n=229) and distribution for the variables studied. The average age of the COPD group and lung cancer group was 69.9 years and 66.7 years respectively. Around half of the COPD group (34%) and lung cancer group (66%) were male. COPD patients were on average overweight (mean BMI 26.1, SD 6.1), with severe or very severe lung function impairment (44% <30%pred), and limited by breathlessness on exertion (57% mMRC 3 or 4) and activities of daily living. Lung cancer patients were younger and had a better performance status than the COPD group, even though over half (55%) had metastatic disease. Fewer data about breathlessness on exertion and lung function were available for the lung cancer group. ADS count was greater in the lung cancer group (mean 4040, SD 2707), compared with the COPD group (mean 2515, SD 1896).

AKPS in COPD

There was a statistically significant positive relationship between AKPS and ADS (r = 0.568, p<0.001, n=74) and 6MWD (r = 0.374, p=0.001, n=76). There was a weak correlation with mMRC (r= -0.022, p=0.850, n=76) and a statistically significant negative relationship BODE score (r=-0.363, p=0.001, n=76).

11/76 (15%)) had a cut-off for AKPS of >70. The ROC curve using ADS showed an area under the curve (AUC) of 0.88 (0.04, 95% CI: 0.79 to 0.97). The optimal ADS cut-point was 3342, which gave a sensitivity of 81.8% and a specificity of 76.2%. The AUC for 6MWD was 0.76 (0.07, 95% CI: 0.62 to 0.90) with an optimal cut off of 242m, which gave a sensitivity of 72.7% and a specificity of 33.9%. The AUC was low for the mMRC (0.44 [0.09], 95% CI: 0.26 to 0.62) and BODE classification (0.27 [0.07], 95% CI: 0.13 to 0.40). (Figure 1).

37/76 (49%)) had a cut-off for AKPS of <60. The ROC curve using ADS had an area AUC of 0.81 (0.06, 95% CI: 0.69 to 0.93). The optimal ADS cut-point was 1333, which gave a sensitivity of 72.1% and a specificity of 76.9%. The AUC for 6MWD was 0.64 (0.09, 95% CI: 0.47 to 0.82), with an optimal cut-point of 203m, which gave a sensitivity of 75.8% and a specificity of 38.5%. The AUC was low for mMRC (0.53 [0.09], 95% CI: 0.36 to 0.71) and for the BODE classification was low (0.37 [0.08], 95% CI: 0.21 to 0.54). The ROC graphs are shown in Figure 1.

AKPS in Lung Cancer

There was a statistically significant relationship between AKPS and ADS (r = 0.499, p<0.001, n=141) and 6MWD (r = 0.916, p<0.001, n=21). Three-quarters (105/140 (75%)) had an AKPS of >70. The ROC curve using ADS showed an AUC of 0.72 (0.04, 95% CI: 0.64-0.81. The optimal ADS cut- point was 3380, which gave a sensitivity of 60.8% with a specificity of 74.4%. The ROC curve is shown in Supplementary Figure 1. For 6MWT the AUC was 1.00. In this sample, there were no patients with AKPS < 60 at baseline.

## DISCUSSION

AKPS (the level of functional independence) is associated with ADS (steps taken in everyday living) and, to a lesser degree, to 6MWD (a measure of functional exercise capacity). In terms of the physical activity measures predicting independent function (AKPS >70), ADS has a better balance of sensitivity and specificity. The AUC for the 6MWD was high but the optimal cut-off demonstrated low specificity. To our knowledge, this is the first study to explore the usefulness of AKPS as an indication of physical activity capacity.

Strengths and limitations of the 6MWD have been reviewed.[2] The distance a patient can walk under test circumstances, does not necessarily relate to the ability to function in everyday activities which requires a broader set of skills and coping mechanisms.

Physical activity measures are good predictors of survival.[12] The discrepancy between "classic" measures assessed in COPD patients like FEV1, 6MWD and patient-centered outcomes like quality of life and activities of daily living has been noted.[12] Few therapeutic trials also measure changes in daily physical activity. Accelerometers might be useful to provide patients with a real-time physical activity feedback, leading to a virtuous circle of maintaining or regaining condition.[13] Consensus about accelerometers and measures is developing.[14]

Strengths and limitations

The combination of data increases generalisability and increased the power of the analysis. However, there was significant missing data for some outcomes of interest. For example, in the COPD group 37.9% of patients had no spirometry values recorded. In the lung cancer group, spirometry was not performed in two-thirds of patients and 6MWD was unavailable in most potentially over-estimating the cut points. Also data regarding stage and previous cancer treatment of lung cancer was missing for some studies. The utility of the 6MWD in people with lung cancer, should be tested on larger datasets. These are cross-sectional data and need confirmation with prospectively collected longitudinal data.

Implications for clinical practice and research

It is important that measures are minimally burdensome and simple to use. Our data indicate that the 6MWT may be less relevant in advanced disease, reflecting other prospective, cross-sectional measures.[15]

The ADS appears to be more useful but may still be impractical for many with advanced disease especially in clinical practice. Our data indicate a useful and strong relationship with AKPS, therefore, if accelerometry is deemed not possible, AKPS would be a useful and practical measure to use instead.

If accelerometry is possible, people whose ADS which falls < 3300 are likely to be those with an AKPS of <70, the level at which independence becomes compromised. Those with an ADS of < 1300 are likely to be those with an AKPS <60; those becoming more unwell and may benefit from palliative care support.

**CONCLUSIONS**

AKPS is strongly related to ADS in people with lung cancer and COPD. ADS may identify patients at risk of losing functional independence and in need of enhanced rehabilitation. The AKPS may be useful in clinical practice and research to indicate levels of physical activity where ADS and 6MWT are not possible.

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Concept and design MJ, MM, DC; data pooling CR, CB; analysis VA, CB; first draft of manuscript CB; all authors contributed substantially to data interpretation, manuscript drafts and approved the final manuscript.

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**ROLE of SPONSOR**

Not applicable for this secondary analysis

**FIGURE LEGENDS**

**Figure 1a:** Receiver Operator Characteristic (ROC) curves for COPD patients calculated with Average Daily Steps, 6MWD and BODE with AKPS score greater than 70.

**Figure 1b:** Receiver Operator Characteristic (ROC) curves for COPD patients calculated with Average Daily Steps, 6MWD and BODE with AKPS score less than 60.

**Online Supplement Figure 1:** Receiver Operator Characteristic (ROC) curves for Lung cancer patients calculated with Average Daily Steps with AKPS score greater than 70.

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**Online Supplement Box 1:** Australia-modified Karnofsky Performance Scale (AKPS) assessment criteria [3]

| **AKPS assessment criteria** | **SCORE** |
|---|---|
| Normal: no complaints; no evidence of disease | 100 |
| Able to carry on normal activity; minor sign of symptoms of disease | 90 |
| Normal activity with effort; some signs or symptoms of disease | 80 |
| Cares for self; unable to carry on normal activity or to do active work | 70 |
| Able to care for most needs; but requires occasional assistance | 60 |
| Considerable assistance and frequent medical care required | 50 |
| In bed more than 50% of the time | 40 |
| Almost completely bedfast | 30 |
| Totally bedfast and requiring extensive nursing care by professionals | 20 |
| and/or family | 10 |
| Comatose or barely rousable | 0 |
| Dead | |

**Online Supplement Table 1. Contributing studies: design, participants, measures**

| Author | Design of study | Participants | Setting | mMRC | AKPS | 6MWD | ADS |
|---|---|---|---|---|---|---|---|
| Johnson MJ et al [4] | RCT phase II international, multicentre, trial efficacy of a hand-held fan and exercise advice with advice alone in increasing activity | N = 49<br>(M/F 26/23)<br>Diagnoses:<br>COPD (55%)<br>Lung Cancer (10%)<br>Asthma (10%)<br>Cardiovascular Disease (8%)<br>Others (17%) | Outpatient | 49 | 49 | 48 | 44* |
| Maddocks M et al [5] | Cohort study, patients randomized to wear ActivePAL 2 vs. 4 vs. 6 days | 60<br>(M/F 40/20)<br>Lung and pleural cancer (97%)<br>Upper Gastro-intestinal cancer (3%) | Outpatient hospital or home visits | 0 | 60 | 0 | 59 |
| Maddocks M et al [6] | RCT, NMES of quadriceps and usual care vs. Usual care | 16<br>(M/F 9/7)<br>Lung and pleural cancer (100%)<br>post-palliative chemotherapy | Cancer clinic, ADS assessed in free living conditions, before RCT intervention | 0 | 16 | 0 | 15 |
| Maddocks M et al [7] | RCT, phase II, double centre NMES of quadriceps and palliative chemotherapy vs | 49<br>(M/F 28/21)<br>Advanced NSCLC (100%) | Inpatient, but ADS assessed in free living conditions, before RCT intervention | 0 | 49 | 0 | 47 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | palliative chemotherapy | | | | | | |
| Maddocks M et al [8] | RCT, double blind, 3 centres, NMES vs placebo | 52 (M/F 21/31) COPD (100%) | Palliative care meetings, pulmonary rehabilitation services. | 49 | 49 | 52 | 49 |
| Ferrioli E et al [9] | Validation of PA monitoring as a responsive outcome measure at different stages of disease | 164 (M/F 69/94) Cancer* 6 (3%) with lung cancer all receiving palliative radiotherapy | Outpatients, candidate to surgery/ chemotherapy /radiotherapy, before intervention | 0 | 53 | 0 | 161 |
| Maddocks M et al [10] | Cross sectional study to investigate skeletal muscle dysfunction | 16 (M/F 7/9) Lung and pleural cancer (100%) palliative chemotherapy, immunotherapy | Outpatients, hospital visits | 16 | 16 | 16 | 16 |

RCT: randomized controlled trial; NMES: neuro-muscular stimulation; COPD: Chronic Obstructive Pulmonary Disease;, mMRC: modified Medical Research Council scale, AKPS: Australian-modified Karnofsky Performance status Scale (research nurse-rated); 6MWD: 6 minute walking test; ADS: average Daily steps measured by accelerometry (* mean of at least 3 days monitoring available across the studies; ActivPAL monitor); NSCLC: non small cell lung cancer * Complete data regarding the primary cancer site was not available; 6 participants known to have lung cancer, all undergoing palliative chemotherapy, were included

**Online Supplement Table 2: Individual pooled data analysis study population (mean (SD) or n (%))**

| | **COPD (n=79)** | **Lung Cancer (n=147)** |
|---|---|---|
| **Gender** | | |
| Male | 36 (45%) | 87 (60%) |
| Female | 43 (55%) | 60 (40%) |
| **Age** (mean (sd) n) | 69.6 (9.4) 79 | 66.7 (9.7) 147 |
| **BMI** (mean (sd) n) | 26.4 (6.1) 52 | 25.5 (4.3) 76 |
| **FEV1%pred** (mean (sd n) | 28.9 (15.1) 49 | 76.7 (25.6) 48 |
| >80% no flow limitation | - | 16 (10.9%) |
| >80% with flow limitation | 1 (1.3%) | 9 (6.1%) |
| 80-50%pred. | 4 (5.1%) | 18 (12.2%) |
| 50-30%pred. | 9 (11.4%) | 5 (3.4%) |
| <30%pred. | 35 (44.3%) | 1 (0.7%) |
| Data not available | 30 (37.9%) | 98 (66.6%) |
| **FVC%pred** (mean (sd) n) | 59.2 (22.3) 49 | 93.7 (27.6) 47 |
| **mMRC** (mean (sd) n) | 2.7 (0.6) 79 | 2.2 (0.8) 21 |
| 1 | - | 4 (2.7%) |
| 2 | 34 (43%) | 8 (5.4%) |
| 3 | 38 (48%) | 9 (6.1%) |
| 4 | 7 (9%) | - |
| Data not available | - (0%) | 126 (85.7%) |
| **AKPS** (mean (sd) n) | 64.7 (10.3) 76 | 81.1 (10.0) 146 |
| 40 | 1 (1.2%) | - |
| 50 | 12 (15.1%) | - |
| 60 | 26 (32.9%) | 7 (4.7%) |
| 70 | 26 (32.9%) | 34 (23.12%) |
| 80 | 9 (11.4%) | 53 (36.05%) |
| 90 | 2 (2.5%) | 41 (27.9%) |
| 100 | - (0%) | 11 (7.5%) |
| Data not available | 3 (3.8%) | 1 (1%) |
| **BODE Index** (mean (sd) n) | 1.7 (1.0) 79 | - |

| | | |
|---|---|---|
| **6MWD** (mean (sd)n) | 216 (96) 79 | 375 (140) 21 |
| **ADS** (mean (sd)) | 2515 (1896) 74 | 4040 (2707) 142 |

BMI Body Mass Index, FEV1 Forced Expiratory Volume in the first second, mMRC modified Medical research Council dyspnoea scale, AKPS Australia-modified Karnofsky Performance Scale, BODE Body-mass index, airflow Obstruction, Breathlessness, and Exercise score, 6MWD 6-minute walking distance