1 **Economic and operational burden associated with malnutrition in chronic obstructive**
2 **pulmonary disease.**

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24 **Key words:** malnutrition, cost analysis, healthcare use, mortality, COPD, chronic obstructive
25 pulmonary disease.

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27 ABSTRACT

28 **Background:** Malnutrition is common in patients with chronic obstructive pulmonary disease
29 (COPD). This study aimed to explore its association with all-cause mortality, emergency
30 hospitalisation and subsequently healthcare costs.

31 **Methods:** A prospective cohort observational pilot study was carried out in outpatients with COPD
32 that attended routine respiratory clinics at a large tertiary Australian hospital during 2011.
33 Electronic hospital records and hospital coding was used to determine nutritional status and whether
34 a patient was coded as nourished or malnourished and information on healthcare use and 1-year
35 mortality was recorded.

36 **Results:** Eight hundred and thirty four patients with COPD attended clinics during 2011, of those
37 286 went on to be hospitalised during the 12 month follow-up period. Malnourished patients had a
38 significantly higher 1-year mortality (27.7% vs. 12.1%; $p = 0.001$) and were hospitalised more
39 frequently (1.11 SD 1.24 vs. 1.51 SD 1.43; $p = 0.051$). Only malnutrition (OR 0.36 95% CI 0.14-
40 0.91; $p = 0.032$) and emergency hospitalisation rate (OR 1.58 95% CI 1.2-2.1; $p = 0.001$) were
41 independently associated with 1-year mortality. Length of hospital stay was almost twice the
42 duration in those coded for malnutrition (11.57 SD 10.93 days vs. 6.67 SD 10.2 days; $p = 0.003$)
43 and at almost double the cost (AUD \$23,652 SD \$26,472 vs. \$12,362 SD \$21,865; $p = 0.002$) than
44 those who were well-nourished

45 **Conclusion:** Malnutrition is an independent predictor of 1-year mortality and healthcare use in
46 patients with COPD. Malnourished patients with COPD present both an economic and operational
47 burden.

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53 INTRODUCTION

54 Disease-related malnutrition is a common problem and presents a significant clinical, economic and
55 operational burden to healthcare systems worldwide. Malnutrition has been suggested to attribute to
56 an increase in hospitalisation costs of 20% [1]. In patients with COPD, up to 60% of inpatients and
57 45% of outpatients have been found to be at risk of malnutrition [2]. According to the Australasian
58 Nutrition Care Day Survey conducted in 56 hospitals across Australia and New Zealand, the overall
59 prevalence of malnutrition was 32% [3]. A previous study also involving 56 hospitals, included
60 6150 Dutch patients and found a quarter of patients to be malnourished but less than half were
61 identified [4]. Malnutrition is associated with several negative clinical outcomes as patients usually
62 have prolonged convalescence from illness, increased length of hospital stay (LOS) and mortality [5
63 6]. Whilst the negative association between nutritional depletion and mortality in COPD is well
64 known [7], the association between malnutrition, healthcare use and the subsequent healthcare costs
65 associated with it in COPD patients has not been fully explored.

66 In Australia, COPD is ranked as having the third highest burden of disease in terms of disability-
67 adjusted life years (DALYs) [8] and affects about 14.5% of all Australian adults above the age of 40
68 [9]. In 2008-2009, health expenditure directly attributed to COPD in Australia was estimated at
69 \$929 million [8] highlighting the economic burden of COPD to the Australian healthcare system.
70 The main treatment goals of COPD are to delay disease progression and reduce the frequency of
71 infective exacerbations [10]. Research has suggested that poor health-related quality of life is
72 associated with the frequency of COPD exacerbations [11] and which is likely to be linked to
73 frequent periods of hospitalisation. In 608 COPD patients hospitalised for an exacerbation in the
74 United Kingdom, patients with a deteriorating nutritional status, indicated by unintentional weight
75 loss exceeding 10% within the 3-6 months preceding the admission, were almost 4-times more
76 likely to be readmitted early [12]. In addition, those patients with a body mass index (BMI) <18.5
77 kg/m² were twice as likely to die during the admission. It is likely that malnutrition is a significant
78 driver of the large burden of COPD to healthcare systems. In the United States it has been estimated

that about 88% of the total direct health expenditure attributed to COPD is associated with acute and ambulatory hospital services [13]. In Australia, inpatient hospital services account for more than half of the direct health expenditure attributed to COPD[8] but to what extent this healthcare use is driven by disease-related malnutrition is unclear. Therefore, this study explored the association between malnutrition in hospitalised COPD patients and its impact on mortality, hospital healthcare use and the subsequent healthcare costs.

METHODS

Study Subjects and Study Design

This study utilised electronic hospital records to identify all of those patients that attending the Respiratory Laboratory at Princess Alexandra Hospital for pulmonary function testing during 2011. All patients who had undertaken at least one lung function test during routine respiratory outpatient clinic attendance with a confirmed diagnosis of COPD were included. COPD patients were identified based on $FEV_1/FVC < 0.7$ and $FEV_1 < 100\%$ predicted. The nutritional status of patients was identified through the diagnosis-related group (DRG) for malnutrition recorded in the hospital records.

Demographic and clinical information such as age, gender, body mass index (BMI), lung function ($\%FEV_1$, $\%DL_{CO}$), and COPD disease severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [14] were collected. Additionally, malnutrition status, 1-year healthcare use and admission data (emergency and elective hospitalisation rate and subsequent duration of hospital stay (LOS) and associated costs (AUD\$)) as well as 1- and 2-year mortality were collected using electronic hospital records. BMI was classified as underweight ($< 21 \text{ kg/m}^2$), normal weight ($21\text{--}25 \text{ kg/m}^2$), overweight ($> 25\text{--}30 \text{ kg/m}^2$) and obese ($> 30 \text{ kg/m}^2$) categories according to the American Thoracic Society/ European Respiratory Society Task Force

104 [15]. Ethical approval for the study was awarded from the hospital Human Research Ethics
 105 Committee and Governance Unit and the Queensland University of Technology (QUT) Research
 106 Ethics Unit (TPCH: HREC/13/QPCH/220, QUT: 1300000774). The reporting of this paper also
 107 conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
 108 recommendations [16]

109 **Nutrition Assessment**

110 In order to receive a DRG code for malnutrition, patient's nutritional status was assessed using the
 111 Subjective Global Assessment (SGA) tool [17] and was completed by a dietitian. The SGA is a
 112 validated nutrition assessment tool which involves a clinical domain: assessing weight and dietary
 113 intake changes over a period of time, nutrition impact symptoms, functional capacity and a physical
 114 assessment domain: assessing fat and muscle wasting, the presence of nutritionally-related oedema
 115 and a patient's functional capacity [17]. The SGA categorises patients into three groups, well-
 116 nourished, mild/moderately malnourished and severely malnourished. Patients diagnosed as
 117 malnourished (mild/moderately or severely malnourished) during their hospital admission were
 118 coded as such using the relevant DRG code.

119 **Healthcare Use**

120 Hospital admission data (frequency, LOS, type (emergency or elective)) and costs were also
 121 collected from electronic hospital records. Costs related to each hospital admission were estimated
 122 using the institution's own health economics modelling techniques which derive costs from DRG
 123 codes. All costs were recorded in Australian Dollars (AUD\$).

124 **Statistical Analysis**

125 Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for
 126 Windows Version 20 (SPSS Inc., Chicago, IL, USA). Continuous variables such as LOS and costs
 127 are presented as mean $\pm$ standard deviation (SD), unless otherwise stated. Categorical variables

such as malnutrition status and 1-year mortality are presented as n (%). A p-value ≤ 0.05 was considered statistically significant.

Differences between two categorical variables were tested using Pearson's chi-square test. Further statistical analyses using purposeful selection with binary logistic regression were also used to predict odds ratios with the associated 95% confidence interval (95% CI) which allowed adjustment for potential confounders associated with mortality. Differences between a categorical and continuous variable were evaluated by comparing their mean $\pm$ SD using one-way ANOVA test. Interrogation of the data in this manner allowed identification of independent associations between malnutrition status, healthcare use, mortality and healthcare costs.

RESULTS

Patient Characteristics

A convenience sample of 834 unique outpatients with a confirmed diagnosis of COPD was obtained. Of those outpatients, 286 went on to experience at least one hospitalisation within a year of their test date which allowed their nutritional status to be identified (Figure 1). Characteristics of the patients included are described in Table 1. Compared to those patients that were not hospitalised (n = 548) the patients included in the study (n = 286) were significantly older (mean age 66.6 SD 11.0 years vs. 64.8 SD 11.7 years; p = 0.030) and had a significantly lower BMI (mean BMI 27.4 SD 6.6 kg/m² vs. 28.6 SD 7.3 kg/m²; p = 0.016) using ANOVA analysis. No differences in lung function between the two groups were observed in terms of Forced Expiratory Volume in 1 second (FEV₁), Diffusing Capacity of the lungs for carbon monoxide (DL_{CO}), FEV₁/FVC ratio, and Residual Volume (RV). Patients coded as malnourished had a significantly lower BMI and there was a trend to be older and have a lower diffusing capacity of the lung (Table 1).

152 **Table 1: Patient characteristics**

Variables	Nourished (n 239)	Malnourished (n 47)	p-value
Male (%): Female (%)	160 (67%):79 (33%)	34 (72%):13 (28%)	0.469
Age (years)	66.1 (11.3)	69.5 (8.7)	0.054
BMI (kg/m ²)	28.2 (6.6)	23.6 (5.4)	<0.001*
FEV ₁ (% predicted)	64.4 (19.6)	60.8 (20.5)	0.260
RV (% predicted)	119.1 (41.0)	123.0 (50.0)	0.691
DL _{CO} (% predicted)	64.4 (20.0)	57.4 (17.6)	0.063

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154 *Results reported are mean (SD) using ANOVA with the exception of age (X^2); BMI = Body Mass*

155 *Index; FEV₁ = Forced Expiratory Volume in 1s; RV = Residual Volume; DL_{CO} = Diffusing*

156 *Capacity of the Lung for Carbon Monoxide; * $p < 0.05$.*

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158 *Malnutrition and mortality*

159 Compared to the nourished patients, patients classified as malnourished had a significantly higher
 160 mortality rate at 1-year (27.7% vs. 12.1%; $p = 0.006$) and this remained the case at 2-years (40.4%
 161 vs. 18%; $p = 0.001$; X^2 analysis). As the malnourished patients tended to be older and have poorer
 162 pulmonary function, binary logistic regression analysis was conducted using purposeful selection
 163 adjusting for potential confounders by exploring the whole cohort of 834 outpatients. Age (p
 164 <0.001), % FEV₁ ($p = 0.019$), BMI ($p = 0.073$) and % DL_{CO} ($p = 0.062$) were all identified as
 165 potential confounders with p values <0.2 and adjusted for within the analysis (Table 2).

166 Malnutrition was found to be a strong independent predictor of 1-year mortality with malnourished
 167 patients having almost three times the odds of dying within a year of their initial presentation (OR
 168 2.93 95% CI 1.10, 7.93; $p = 0.009$). Other than malnutrition, the only other variable found to be
 169 significantly and independently associated with 1-year mortality was emergency hospitalisation

rate. BMI, %FEV₁, %DL_{CO}, COPD severity and age were not associated with 1-year mortality in regression analysis.

Table 2: Binary logistic regression for predictors of 1-year mortality

Variables	Odds Ratio [95%CI]	p-value
Number of Emergency Admissions	1.55 [1.19, 8.69]	<0.001*
Malnutrition	2.93 [1.10, 7.93]	0.009*
Age	1.04 [0.99, 1.10]	0.120
BMI	0.99 [0.97, 1.02]	0.484
% DL _{CO}	0.99 [0.97, 1.02]	0.507
% FEV ₁	0.98 [0.92, 1.04]	0.610
COPD disease-severity (GOLD)	0.59 [0.13, 2.67]	0.935

*BMI = Body Mass Index; FEV₁ = Forced Expiratory Volume in 1s; DL_{CO} = Diffusing Capacity of the Lung for Carbon Monoxide; * p < 0.05.*

Similar results were obtained when analysis of time to event was performed using cox-regression survival analysis (Figure 2). Malnutrition (OR 0.42 95% CI 0.19 to 0.91; p = 0.028) and emergency hospitalisation rate (OR 1.37 95% CI 1.15 to 1.62; p < 0.001) remained significant independent predictors of mortality.

Malnutrition and costs associated with hospitalisation

Following emergency hospital admission, malnourished patients were found to have a significantly longer LOS than nourished patients; mean LOS 11.57 SD 10.94 days vs. 6.67 SD 10.21 days; difference +4.9 SE 1.65 days 95%CI 1.65-8.15 days; p = 0.003. Similar results were also found when emergency and elective lengths of stay were combined (malnourished 22.51 SD 19.40 days

187 vs. nourished 11.26 SD 14.67 days; difference +11.3 SE 2.48 days 95%CI 6.4-16.1 days; $p < 0.001$).

188 With malnourished patients remaining hospitalised for almost twice the duration as nourished

189 patients, the resulting costs were also significantly higher in the malnourished group; mean cost

190 \$23,652 SD \$26,472 vs. \$12,362 SD \$21,865; difference +\$11,290 SE \$3,618 95%CI \$4,168-

191 \$18,411; $p = 0.002$ (Figure 3). Similar results were also found when analysing the costs associated

192 with non-emergency admissions (malnourished \$38,833 SD \$25,770 vs. nourished \$21,468 SD

193 \$27,747; difference +\$17,365 SD \$4,659 95% CI \$8,195-\$26,535; $p < 0.001$).

194 **DISCUSSION**

195 This is the first study to evaluate the impact of malnutrition on hospitalisation, healthcare costs and

196 mortality in patients with COPD. Malnutrition was found to be a significant and independent

197 predictor of mortality, with malnourished patients almost three times greater odds of dying within a

198 year. Whilst the negative association between nutritional depletion and survival in COPD is well

199 known, previous survival analysis has shown that appropriate nutritional therapy resulting in weight

200 gain is associated with improved survival [18]. However, it is yet to be established whether

201 improved survival following the treatment of malnutrition is also associated with reduced healthcare

202 use. In the current study, patients coded as malnourished during their hospital admission remained

203 hospitalised for almost twice the duration as their nourished counterparts, at almost double the cost.

204 Whilst previous studies have not formally diagnosed malnutrition, they have reported nutrition

205 status, defined by various means, to be associated with increased mortality and healthcare use. In a

206 study of patients requiring long-term oxygen therapy, a BMI $< 20 \text{ kg/m}^2$ was found to be an

207 independent risk factor for increased mortality and hospitalisation [19]. Analysis of COPD patients

208 from the Copenhagen City Heart Study reported BMI to be independently associated with all-cause

209 mortality [20]. More recent retrospective cohort study involving over 300,000 COPD hospital

210 admissions discovered obese patients to have lower in-hospital mortality and a lower risk of early

211 readmission compared to non-obese patients [21]. The authors also found that non-obese patients

212 had a considerably higher risk of mortality during hospitalisation and readmission within 30 days of
213 discharge. However, full nutritional assessment and malnutrition status was not assessed.

214 With an increased focus on reducing the duration of hospital stay and avoidance of hospital
215 readmission, all but the sickest patients are managed in the outpatient setting. This reduces the
216 opportunity within which hospitalised COPD patients at nutritional risk can be identified, seen by a
217 dietitian for nutritional assessment and the initiation and evaluation of individualised nutritional
218 support. In order for this to occur, robust policies documenting the nutritional management of
219 COPD patients are required. The first step is for malnourished patients to be promptly identified,
220 either in the community or on admission. Whilst there is currently no universally accepted method
221 for the identification of malnutrition, there are several validated nutritional screening and
222 assessment tools available. Most nutritional screening tools involve an assessment of recent
223 unintentional weight loss and BMI is also often recommended as a routine marker of nutritional
224 status [22 23]. However, there is no consensus around what the BMI cut-off for nutritional risk in
225 COPD should be, with recommendations of $<20 \text{ kg/m}^2$ (NICE [23]) and $<21 \text{ kg/m}^2$ (ATS/ERS [22]
226 and BODE index [20 24]). In addition, it appears that there are currently no guidelines around the
227 management of COPD that formally recommend routine nutritional screening and nutritional
228 assessment. Whilst BMI has good predictive validity for survival and hospitalisation [19] and is a
229 pragmatic measurement routinely advocated by guidelines, it is not without its limitations.

230 Depletion of fat-free mass that is common in COPD [25] can be masked by an expansion of fat-
231 mass impacting on the sensitivity of BMI as a marker of nutritional depletion and risk. This was
232 highlighted in a study of 300 outpatients with COPD where a BMI $<20 \text{ kg/m}^2$ was reported in 17%
233 of patients but more than double (38%) had fat-free mass depletion [26]. If BMI alone is used as a
234 method of identifying nutritional risk, a significant proportion of patients would go unidentified.

235 Indeed, a recent review by Schols et al., [27] suggests that fat-free mass might be a better predictor
236 of mortality in COPD patients than BMI alone. The current study found BMI to be a less sensitive

237 predictor of survival, rather rate of emergency hospitalisation and comprehensive nutritional
238 assessment allowing diagnosis of malnutrition had much stronger associations with poor survival.

239 The current findings that malnourished COPD patients experience greater emergency healthcare use
240 and longer durations of hospital stay are consistent with previous studies in other patient groups that
241 have reported prolonged LOS [28-30], higher rate of readmission rates[28 29], increased pressure
242 ulcer incidence and delayed wound healing [5 31]. However, it is often thought that malnutrition is
243 a consequence of the progressive pathophysiology associated with COPD; with those with the more
244 severe disease having poorer respiratory function and elevated inflammatory processes contributing
245 towards the development of malnutrition and subsequent poorer survival [7]. The current study
246 attempted to account for this by adjusting for COPD disease severity, age and lung function, finding
247 that only malnutrition and emergency hospitalisation rate to be independently associated with
248 poorer survival. Due to the observational nature of the study, it is the difficult to establish exact
249 causation between the two independent predictors and whether patients are more likely to become
250 malnourished following recurrent bouts of emergency hospitalisation or whether those patients with
251 malnutrition more likely to have infective exacerbations of COPD requiring hospitalisation. The
252 aetiology of malnutrition in COPD is multi-factorial and complex and both are likely to be related.
253 However, recent systematic review and meta-analyses have shown that if malnutrition is identified
254 in COPD, it is amenable to treatment, resulting in significantly improved nutritional status,
255 functional capacity and associated with improvements of quality of life [32 33]. Interestingly, the
256 reviews found that nutritional support in stable COPD outpatients resulted in an increase in body
257 weight of approximately 2kg and it is this level of weight gain that has previously been associated
258 with improved survival in malnourished COPD patients [18]. Whilst the evidence base for
259 nutritional intervention in stable (non-exacerbating) outpatients with COPD is strong, it is almost
260 entirely based on liquid pre-prepared oral nutritional supplements (ONS). There is limited evidence
261 demonstrating the effectiveness of other forms of nutritional intervention such as fortified meals
262 and dietary counselling provided by a dietitian. However, this lack of evidence does not indicate a

263 lack of effect. Also, few studies have attempted to investigate the effectiveness of nutritional
264 support in acutely unwell hospitalised COPD patients. One reason for this is the difficulty in
265 intervening in an acute unwell population with a relatively short length of admission. Whilst the
266 average hospital length of stay for the nourished patients in the current study was less than a week,
267 the malnourished patients tended to stay on average 5 days longer. Vermeeren et al., [34] found that
268 whilst nutritional support using ONS was able to significantly increase energy and in particular
269 protein intake during the average 9 days admission period it did not lead to any improvements
270 above that of the control group. The authors highlight the difficulty in achieving theoretical
271 nutritional requirements during an infective exacerbation through the normal hospital diet alone
272 without nutritional support. It is likely that nutritional interventions need to be longer in duration for
273 improvements to be seen with studies in stable COPD outpatients usually lasting between 8-12
274 weeks [33]. A previous study by Weekes et al., [35] involving stable malnourished outpatients with
275 COPD found dietetic counselling over 6 months not only resulted in significant improvements in
276 nutritional status and quality of life but these improvements remained at 12 months. However,
277 further research is needed to establish whether nutritional interventions initiated promptly on
278 admission in malnourished COPD patients, and continued for an appropriate period of time, can
279 lead to improvements in nutritional status and reduced subsequent healthcare use and costs.

280 Whilst the current study involved a large enough sample size to perform regression analysis
281 adjusting for confounders, it isn't without limitations. Although a large sample, it is from a single
282 large tertiary hospital. Therefore extrapolation of results should be done with caution. Electronic
283 medical record data on hospitalisation and duration of stay was only available for that hospital site
284 and if patients were admitted to surrounding hospitals this information would not have been
285 captured. The current sample was also limited by the fact that comprehensive nutritional assessment
286 and the diagnosis of malnutrition was only possible in those patients admitted to hospital. Current
287 local policy meant that routine nutritional screening was not part of outpatient clinical
288 appointments. The prevalence of malnutrition in the 286 patients that went on to experience a

289 hospital admission in the current study at 16%, whilst this is comparable to previous rates reported
 290 of 19% [36] and 24% [37] these studies used a BMI threshold of $<20 \text{ kg/m}^2$. As the current study
 291 used full nutritional assessment using the Subjective Global Assessment, 16% would appear to be
 292 an underestimate of the true malnutrition prevalence. In a study that used BMI and assessment of
 293 FFM to diagnose malnutrition the prevalence was 38% [38]. It is possible patients were not
 294 documented on the electronic hospital records as malnourished, this is common in COPD and has
 295 been found to be the case in another Australian hospital [39]. However, it is felt that undiagnosed
 296 malnutrition in the current study will only have had the potential to reduce the magnitude of the
 297 current estimates and we feel the conclusions would remain unchanged.

298 In conclusion, disease-related malnutrition in COPD is independently associated with a significant
 299 clinical, economic and operational burden to hospitals. Malnutrition and emergency hospitalisation
 300 was also associated with poorer survival. Whilst malnutrition in COPD patients has been found to
 301 be amenable to treatment through nutritional support, the evidence is almost entirely based on stable
 302 outpatients and it is hoped future well-designed prospective nutritional intervention studies will
 303 explore the impact of early nutritional assessment and nutritional interventions on clinical and
 304 economic outcomes.

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