

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

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

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23  
24 **Key words:** malnutrition, cost analysis, healthcare use, mortality, COPD, chronic obstructive  
25 pulmonary disease.

26

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/m<sup>2</sup> 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

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

85

86

## 87 **METHODS**

### 88 **Study Subjects and Study Design**

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

96 Demographic and clinical information such as age, gender, body mass index (BMI), lung function  
97 ( $\%FEV_1$ ,  $\%DL_{CO}$ ), and COPD disease severity according to Global Initiative for Chronic  
98 Obstructive Lung Disease (GOLD) classification [14] were collected. Additionally, malnutrition  
99 status, 1-year healthcare use and admission data (emergency and elective hospitalisation rate and  
100 subsequent duration of hospital stay (LOS) and associated costs (AUD\$)) as well as 1- and 2-year  
101 mortality were collected using electronic hospital records. BMI was classified as underweight  
102 ( $< 21 \text{ kg/m}^2$ ), normal weight ( $21\text{-}25 \text{ kg/m}^2$ ), overweight ( $> 25\text{-}30 \text{ kg/m}^2$ ) and obese ( $> 30 \text{ kg/m}^2$ )  
103 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

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

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

## 137 **RESULTS**

### 138 **Patient Characteristics**

139 A convenience sample of 834 unique outpatients with a confirmed diagnosis of COPD was  
140 obtained. Of those outpatients, 286 went on to experience at least one hospitalisation within a year  
141 of their test date which allowed their nutritional status to be identified (Figure 1). Characteristics of  
142 the patients included are described in Table 1. Compared to those patients that were not hospitalised  
143 (n = 548) the patients included in the study (n = 286) were significantly older (mean age 66.6 SD  
144 11.0 years vs. 64.8 SD 11.7 years; p = 0.030) and had a significantly lower BMI (mean BMI 27.4  
145 SD 6.6 kg/m<sup>2</sup> vs. 28.6 SD 7.3 kg/m<sup>2</sup>; p = 0.016) using ANOVA analysis. No differences in lung  
146 function between the two groups were observed in terms of Forced Expiratory Volume in 1 second  
147 (FEV<sub>1</sub>), Diffusing Capacity of the lungs for carbon monoxide (DL<sub>CO</sub>), FEV<sub>1</sub>/FVC ratio, and  
148 Residual Volume (RV). Patients coded as malnourished had a significantly lower BMI and there  
149 was a trend to be older and have a lower diffusing capacity of the lung (Table 1).

150

151

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 <sup>2</sup> )	28.2 (6.6)	23.6 (5.4)	<0.001*
FEV <sub>1</sub> (% predicted)	64.4 (19.6)	60.8 (20.5)	0.260
RV (% predicted)	119.1 (41.0)	123.0 (50.0)	0.691
DL <sub>CO</sub> (% predicted)	64.4 (20.0)	57.4 (17.6)	0.063

153

154 *Results reported are mean (SD) using ANOVA with the exception of age ( $X^2$ ); BMI = Body Mass*155 *Index; FEV<sub>1</sub> = Forced Expiratory Volume in 1s; RV = Residual Volume; DL<sub>CO</sub> = Diffusing*156 *Capacity of the Lung for Carbon Monoxide; \* p < 0.05.*

157

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), % FEV<sub>1</sub> (p = 0.019), BMI (p = 0.073) and % DL<sub>CO</sub> (p = 0.062) were all identified as

165 potential confounders with p values &lt;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



170 rate. BMI, %FEV<sub>1</sub>, %DL<sub>CO</sub>, COPD severity and age were not associated with 1-year mortality in  
 171 regression analysis.

172 **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 <sub>CO</sub>	0.99 [0.97, 1.02]	0.507
% FEV <sub>1</sub>	0.98 [0.92, 1.04]	0.610
COPD disease-severity (GOLD)	0.59 [0.13, 2.67]	0.935

173

174 *BMI = Body Mass Index; FEV<sub>1</sub> = Forced Expiratory Volume in 1s; DL<sub>CO</sub> = Diffusing Capacity of*  
 175 *the Lung for Carbon Monoxide; \* p < 0.05.*

176

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

181

### 182 **Malnutrition and costs associated with hospitalisation**

183 Following emergency hospital admission, malnourished patients were found to have a significantly  
 184 longer LOS than nourished patients; mean LOS 11.57 SD 10.94 days vs. 6.67 SD 10.21 days;  
 185 difference +4.9 SE 1.65 days 95%CI 1.65-8.15 days; p = 0.003. Similar results were also found  
 186 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 kg/m<sup>2</sup> 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.

305

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