Healthcare utilization, medical costs and mortality associated with malnutrition in patients with chronic obstructive pulmonary disease: a matched cohort study

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ABSTRACT
Objective: Although disease-related malnutrition has prognostic implications for patients with chronic obstructive pulmonary disease (COPD), its health-economic impact and clinical burdens are uncertain. We conducted a population-level study to investigate these questions.

Methods: We excerpted data relevant to malnutrition, prolonged mechanical ventilation and medications from claims by 1,197,098 patients who were consistent with COPD and registered by the Taiwan National Health Insurance Administration between 2009 and 2013. These patients were separated into cohorts with or without respiratory failure requiring long-term mechanical ventilation, and each cohort was divided to compare cases who developed malnutrition after their first diagnosis consistent with COPD, versus non-malnourished propensity-score matched controls.

Results: The prevalence of malnutrition was 3.8% overall (10,259/287,000 non-ventilator-dependent; 1198/15,829 ventilator-dependent). Propensity-score matched non-ventilator-dependent patients who became malnourished (N = 10,242) had comparatively more hospitalizations, emergency room and outpatient visits, longer hospitalization (all p < .01), and higher mortality (HR = 2.26, 95% CI 2.18–2.34) than non-malnourished controls (N = 40,968). Malnourished ventilator-dependent patients (N = 1197) had higher rates of hospitalization, emergency room and outpatient visits, but shorter hospitalization (all p < .001) and lower mortality (HR = 0.85, 95% CI 0.80–0.93) than matched non-malnourished controls (N = 4788). Total medical expenditure on malnourished non-ventilator-dependent COPD patients was 75% higher than controls (p < .001), whereas malnourished ventilator-dependent patients had total costs 7% lower than controls (p < .001).

Conclusions: Malnourishment among COPD patients who were not dependent on mechanical ventilation was associated with greater healthcare resource utilization and higher aggregate medical costs.

1. Introduction

Malnutrition is “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease”1. There is a growing body of research on the burden that malnutrition imposes on patients and healthcare systems2,3. The detrimental impacts of disease-related malnutrition are compounded by its high prevalence and association with suboptimal functional recovery and poor survival4. Malnourished people are more likely than are non-malnourished counterparts to be hospitalized, have complications and to die5. Malnutrition also imposes considerable financial costs, accounting for between 2% and 10% of annual national healthcare expenditure in European countries6,7 and the United States3,8. In general, malnourished patients receiving medical or surgical treatment had 55% higher medical costs than those without malnutrition, besides having longer hospital stays and needing more care9,10.

Chronic obstructive pulmonary disease (COPD) is increasingly recognized as an important problem, due to its heavy healthcare burden worldwide11,12; moreover, becoming malnourished might worsen COPD. In a United Kingdom survey of outpatients with COPD, up to 21% were at risk for malnutrition, most of whom were likely to need nutritional treatment, and the overall prevalence of malnutrition increased with COPD severity13; the outpatients at risk of malnutrition had more hospital admissions and were more likely to die within 6 months14. Others have reported that COPD is commonly accompanied by nutrition impact symptoms, which are more severe in nutrition-depleted individuals15. Although undernourishment does not contribute to diaphragm weakness in patients with COPD16, they have protein metabolism abnormalities that contribute to skeletal muscle alteration17. Severe COPD and advancing age can independently

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contribute to malnutrition. Poor lung function and impaired exercise tolerance were associated with a high prevalence of malnutrition among hospitalized COPD patients, while nutritional status in patients with a COPD exacerbation was related to the duration of hospitalization and the readmission rate. In another study, hospitalized patients with COPD who were underweight or lost weight during follow-up had a higher risk of new exacerbations. Given that COPD patients are known to have systemic comorbidities such as deconditioning, exercise intolerance, skeletal muscle dysfunction, osteoporosis, metabolic impact, anxiety and depression, and cardiovascular disease, with consequently high mortality, it is important to recognize malnutrition early so that timely intervention can be instituted.

Although malnutrition is associated with inimical outcomes in COPD, the magnitude of its overall impact is unknown; most reports on the health-economic burden of malnutrition have been based on data from single institutes or regional registries, with cohorts involving predominantly hospitalized patients. Public sector healthcare in Taiwan is reimbursed by universal National Health Insurance (NHI), which covers outpatient, inpatient and emergency care. Patients with acute respiratory failure are initially admitted to an intensive care unit (ICU) and treated with mechanical ventilators. NHI policy is to transfer patients with respiratory failure who have used mechanical ventilation for more than 21 days to a step-down respiratory care center and onward to a general respiratory care ward (unless there is specific indication for remaining in the ICU or subsequent readmission). Patients receiving mechanical ventilation who have chronic respiratory failure can be discharged to home ventilator use, which NHI also covers. To investigate the importance of malnutrition in patients with COPD at the population level, we used the well validated Taiwan NHI claims database to quantify the impact of malnutrition on healthcare utilization and medical costs.

2. Methods

2.1. Study design, setting and purpose

This study analyzed data excerpted retrospectively from the Taiwan NHI Research Database (NHIRD), to investigate the impact of malnutrition on clinical and health-economic outcomes in patients with COPD.

2.2. Participant selection and outcome variables

Figure 1 shows the patient selection flow, and results of propensity-score matching: COPD cases from 1 January 2009 through 31 December 2013 were selected from NHIRD claims data, based on International Classification of Diseases 9th edition (ICD-9-CM) codes.
COPD was defined as insurance claims documentation of three consecutive outpatient visits or a single hospitalization with an ICD-9-CM code compatible with COPD (490.X and 496; Supplementary Table S1); the date participants were first given such an ICD-9-CM code was defined as the index date. Potentially eligible patients were subdivided into those with a catastrophic illness registration denoting respiratory failure requiring prolonged mechanical ventilation (ICD-9-CM 518.85; Supplementary Table S1) and those without respiratory failure (most of whom were not dependent on mechanical ventilation). This classification was based on the Taiwan NHI policy that patients who are dependent on mechanical ventilation (i.e. invasive or non-invasive mechanical ventilation for ≥21 days) can apply for a catastrophic illness certificate that exempts them from co-payments for outpatient or inpatient care. We reasoned that the care settings of patients with versus without ventilator dependence would probably differ, resulting in different treatment costs for either subgroup of patients. Patients who did not fulfill the eligibility criteria were excluded, as were those with an index date during 2009, to ensure that their clinical features and comorbidities had existed for at least 1 year preceding the index date. History of malnutrition was based on ICD-9-CM–compatible codes during 1 year preceding the index date that included: 260–262, 263.0, 263.2, 263.8, 263.9, 265.X, 266.X and 268.X, which have been shown to adequately cover the clinical manifestations of malnutrition and 799.X, based on experience that clinicians might also use these codes to designate malnutrition in certain circumstances, such as cachexia.

Patients with or without ventilator dependence who were diagnosed with malnutrition after the index date (based on the aforementioned ICD-9-CM codes) constituted cases. We calculated the Charlson Comorbidity Index (CCI) scores based on comorbidity profiles during the year before the index date. Logistic regression was used to model the risk of mortality in patients with or without ventilator dependence as a function of demographic characteristics (age, sex, residential location), comorbidity profile and CCI scores. Based on the regression results, a 1:4 propensity-score matched control group for cases was identified using an established procedure, with a balanced distribution of covariates among patients with/without malnutrition in the groups with/without ventilator dependence, based on the nearest-neighbor approach.

We excerpted demographic information, diagnosis records and NHI claims data relevant to healthcare utilization and clinical outcomes for both malnourished cases and non-malnourished controls from either analytic cohort with or without ventilator dependence, from the index date until death or 31 December 2013, whichever occurred first. The primary outcome was healthcare resource utilization, including annual numbers of outpatient and emergency room visits, frequency and duration of hospitalization, and claim-based aggregate costs associated with medical care from the index date until the end of follow-up, converted from New Taiwan Dollars at the time of analysis to 2013 United States dollars. We also estimated survival at 4-year follow-up for propensity-score matched malnourished cases and non-malnourished controls in the ventilator-dependent and non-ventilator dependent cohorts.

2.3. Statistics

Statistical analyses were performed using R-2.11.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria), run on Microsoft Windows 7 Operating System. We compared demographic features of patients with versus without malnutrition before re-grouping by propensity-score matching. For clinical features including demographic and comorbidity data, and all outcomes, continuous variables were expressed as mean and standard deviation (SD), compared using Student’s t-test. Categorical variables were expressed as percentages, and compared using the chi-square test. After propensity-score matching, we analyzed healthcare utilization and costs by applying a two-part model process. Logistic regression was applied to predict the probability of healthcare service utilization, whereas a generalized linear model was used to predict the frequency of healthcare utilization and costs among those with visits or hospital admissions. Covariates entered into the models to predict the healthcare utilization included age, sex and residential area urbanization level. We then used t-tests to examine differences in the regression-adjusted frequency of healthcare utilization and costs between cases and controls. We used Kaplan–Meier analysis to plot survival curves based on the absence or presence of malnutrition in COPD patients with versus without ventilator dependence and compared the results with a log-rank test. Cox proportional hazard regression analysis, incorporating socio-demographic variables, CCI and malnutrition, was applied to assess the relationship between malnutrition and mortality in COPD patients with versus without ventilator dependence.

2.4. Ethical compliance

National Taiwan University Hospital Research Ethics Committee approved the study protocol (#201503028W) and waived the requirement for informed consent, based on the anonymity of NHIRD records.

3. Results

Between 2009 and 2013 the Taiwan NHIRD recorded insurance claims made by 1,197,098 patients who had ICD-9-CM codes compatible with COPD; Figure 1 shows the patient selection flowchart. The analytic cohort without ventilator dependence, selected by applying the inclusion/exclusion criteria from among 1,123,790 patients prescribed medications for COPD, comprised 287,000 patients, of whom 10,259 (3.6%) had malnutrition. From another 73,308 patients with ICD-9-CM codes compatible with both COPD and respiratory failure, 57,479 were excluded and a second analytic cohort included 15,829 ventilator-dependent patients, 1198 (7.6%) of whom had malnutrition. In total, 11,457 of 302,829 patients in both analytic cohorts had malnutrition, a...
prevalence rate of 3.8%. Table 1 summarizes the demographic and baseline clinical characteristics of the selected patient cohorts with or without ventilator dependence before propensity-score matching. In the non-ventilator-dependent cohort, patients with malnutrition were older, predominantly male and proportionally more had CCI > 2 (all \( p < .001 \)) compared to non-malnourished ones. In contrast, malnourished patients in the ventilator-dependent cohort had sex ratios similar to those without malnutrition, but were significantly younger (\( p = .005 \)), and a smaller proportion had CCI > 2 (\( p = .010 \)).

After 1:4 propensity-score matching, the non-ventilator-dependent cohort comprised 10,242 malnutrition cases and 40,968 non-malnourished controls, while the ventilator-dependent cohort comprised 1197 cases with malnutrition and 4788 controls (Figure 1). Malnutrition cases and non-malnourished controls had generally similar socio-demographic and comorbidity profiles (Table 2); however, there were some statistically significant differences. In the matched non-ventilator-dependent cohort, COPD patients with malnutrition had a higher prevalence of congestive heart failure (\( p = .028 \)) than controls, and significantly higher rates of cerebral vascular disease, dementia, peptic ulcer, diabetes and cancer (all \( p < .001 \)). Malnourished cases in the matched ventilator-dependent COPD cohort had proportionally more diabetes with end-organ damage compared to controls (\( p = .003 \)), but similar proportions of other comorbidities.

Table 3 and Figures 2 and 3 show the 4-year outcomes in the ventilator-dependent and non-ventilator-dependent propensity-score matched cohorts. Compared to non-ventilator-dependent controls, malnourished patients had more hospitalizations, emergency room and outpatient visits, and days hospitalized, amounting to 9.7% of total patient-years hospitalized during the observation period, versus 6.7% for controls (all \( p < .001 \)) (Figure 2, Table 3). Malnourished patients in the matched ventilator-dependent COPD cohort likewise had more hospitalizations, emergency room and outpatient visits than controls; however, they were hospitalized for fewer days on average and 46.8% versus 52.1% of total patient-years (all \( p < .001 \)) (Figure 2, Table 3). Malnourished patients in the matched non-ventilator-dependent cohort had higher rates of total mortality and inhospital mortality than non-malnourished controls, and almost double the total medical costs (all \( p < .001 \)), whereas...
Table 3. Readmission, hospitalization and mortality rates of each propensity-score matched COPD cohort.

| Variable                              | Non-ventilator-dependent | Ventilator-dependent | p    | Cases | Controls | p    |
|---------------------------------------|--------------------------|----------------------|------|-------|----------|------|
| Number                                | 10,242                   | 40,968               |      |       | 1197     | 4788 |
| Readmission rate per 30 days          | 2443/6184 (39.5%)        | 5109/14,153 (35.2%)  | <.001| 447/750 (59.6%) | 1454/2432 (59.8%) | .928 |
| Number hospitalized                   | 8765 (85.8%)             | 26,457 (64.6%)       |      | 1192 (99.6%) | 4770 (99.6%) |     |
| Proportion of total observation period hospitalized (patient-years) | 1737/17,823 (9.7%) | 3772/60,479 (6.0%) | <.001 | 748/1597 (46.8%) | 2946/5659 (52.1%) | <.001 |
| Total deathsa                         | 4731                     | 9554                 | <.001| 818   | 3331     | <.001|
| Deaths in hospitalb                   | 2963                     | 6930                 | <.001| 578   | 2751     | <.001|
| Mortality rate per person-yeara       | 26.5%                    | 15.8%                |      | 51.2% | 58.9%    |     |
| In-hospital mortality rate per person-yearb | 16.7%                 | 11.5%                |      | 36.2% | 48.6%    |     |

Abbreviations. COPD, Chronic obstructive pulmonary disease; SD, Standard deviation.

*aBased on Taiwan National Health Insurance hospitalization claims: “Death in catastrophic illness”, “Insurance data termination with no medical records”, or discharge record of death or being terminally ill and critically discharged.

*bBased on Taiwan National Health Insurance hospitalization claims discharge record as death or being terminally ill and critically discharged.

Figure 2. Comparison of healthcare resource utilization between malnourished versus non-malnourished patients with COPD in cohorts with or without dependence on mechanical ventilation. Abbreviation. ER, Emergency room. *p < .001.
malnourished patients in the matched ventilator-dependent cohort had lower rates of total and in-hospital mortality, and slightly lower costs than controls (all \( p < .001 \)) (Figure 3, Table 3).

Cox proportional hazard analysis showed that malnutrition independently increased the risk for mortality in propensity-score matched non-ventilator-dependent patients \( (p < .001) \), whereas malnutrition in the ventilator-dependent cohort was associated with a lower risk for mortality \( (p < .001) \) (Table 4). Both cohorts showed an increasing likelihood of death with advancing age, with men more likely than women to die.

4. Discussion

Among this nationally representative patient sample, the prevalence of malnutrition after the index date of receiving an ICD-9-CM diagnostic code consistent with COPD was 3.8%. Malnutrition increased healthcare resource utilization and costs, as well as mortality, among COPD patients who were not ventilator dependent. Incongruently, malnutrition in patients with COPD who required prolonged mechanical ventilation was associated with slightly lower overall medical costs and better prognosis. This study, based on national
The evident association between malnutrition and dementia and depression accounting for cost 15 billion dollars in the United States, with malnourished patients with COPD, but also imply that this correlation is stronger among those without prolonged ventilator dependence. Disease-related malnutrition has been estimated to cost 15 billion dollars in the United States, with malnourished patients with dementia and depression accounting for 10 billion. The evident association between malnutrition and healthcare utilization by patients with COPD in our study, especially among non-ventilator-dependent patients, was commensurate with previous studies in other patient populations. On the other hand, our finding that malnourished patients who were ventilator dependent had slightly lower medical costs and mortality than adequately nourished counterparts suggests a less straightforward relationship between nutritional status and health outcomes in such patients. One explanation is that the high NHI cost of reimbursing long-term mechanical ventilation might overshadow that imposed by malnutrition. Collectively, these population-based findings warrant clinical trials of early interventions to prevent malnourishment and improve nutrition in COPD patients.

More than double the risk for mortality in non-ventilator-dependent COPD patients with malnutrition highlights the importance of research to understand better how malnutrition interacts with COPD in this setting. Malnutrition in COPD patients with chronic respiratory failure is strongly related to hyperinflation, and non-invasive ventilator treatment in malnourished patients resulted in significant weight gain. In another study, a high-fat, low-carbohydrate oral supplement improved pulmonary function in patients with COPD significantly compared with a conventional high-carbohydrate diet. Malnutrition is also known to play an important role in how elderly individuals with COPD perceive their symptoms. Elderly patients with COPD might complain of lacking energy, which is one of eight items assessed by the COPD Assessment Tool; however, the utility of this metric for additional diagnosis of malnutrition remains unclear. As current clinical guidelines for COPD make few recommendations regarding nutrition, we advocate further research to investigate how malnutrition contributes to increased risk of mortality in patients with COPD, and trials to evaluate the effects of systematic screening and early intervention to prevent malnutrition in patients with COPD.
malnutrition may be under-diagnosed, and assessing its impact more accurately might require further research. Nevertheless, malnutrition prevalence of 3.8% in patients with COPD is commensurate with other reports. Furthermore, this methodology would allow comparisons across different patient populations and countries based on the same ICD-9-CM coding. Third, mortality was documented indirectly, based on NHI hospitalization claims data; nevertheless, since Taiwan NHI covers almost all healthcare expenses, most deaths among included patients would be counted. Fourth, malnutrition severity was not assessed, which precluded quantitative estimation of the differential impact of increasingly severe malnutrition on healthcare utilization and burden. Therefore, although this study highlights the significant impact of malnutrition in COPD patients, further research is required to ascertain the magnitude of its impact. Last, we were unable to investigate the role of nutritional supplementation because the NHIRD does not record this information. The main potential biases included the probability of comorbidities that might also entail resource use and associated care costs because patients with COPD have a high probability of comorbidities during their disease course. Although the costs in a substantial proportion of patients in this study group might not be attributed to COPD alone, the propensity-score matching design eliminated this problem in comparisons between patients with and without malnutrition.

5. Conclusions

This population-based study of a nationally representative cohort of patients with COPD affirms that non-ventilator-dependent patients with malnutrition use more healthcare resources, impose higher healthcare costs and have worse survival than those who are not malnourished. Our findings highlight the priority of diagnosing malnutrition in patients with COPD early, and of implementing prompt and timely management to diminish its associated healthcare burdens.

Transparency

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Author contributions

J.S.J., R.W.Y.C. and M.Y.H.W. participated in analyzing and interpreting data and preparing the manuscript. C.H.T. and R.W.Y.C. excerpted data. C.H.T. and K.Y.H. critically reviewed the work and approved the final version of the manuscript.

Declaration of financial/other relationships

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