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Effect of Hospital Use of Oral Nutritional Supplementation on Length of Stay, Hospital Cost, and 30-Day Readmissions Among Medicare Patients With COPD

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BACKGROUND: COPD is a leading cause of death and disability in the United States. Patients with COPD are at a high risk of nutritional deficiency, which is associated with declines in respiratory function, lean body mass and strength, and immune function. Although oral nutritional supplementation (ONS) has been associated with improvements in some of these domains, the impact of hospital ONS on readmission risk, length of stay (LOS), and cost among hospitalized patients is unknown.

METHODS: Using the Premier Research Database, we first identified Medicare patients aged ≥ 65 years hospitalized with a primary diagnosis of COPD. We then identified hospitalizations in which ONS was provided, and used propensity-score matching to compare LOS, hospitalization cost, and 30-day readmission rates in a one-to-one matched sample of ONS and non-ONS hospitalizations. To further address selection bias among patients prescribed ONS, we also used instrumental variables analysis to study the association of ONS with study outcomes. Model covariates included patient and provider characteristics and a time trend.

RESULTS: Out of 10,322 ONS hospitalizations and 368,097 non-ONS hospitalizations, a one-to-one matched sample was created (N = 14,326). In unadjusted comparisons in the matched sample, ONS use was associated with longer LOS (8.7 days vs 6.9 days, $P < .0001$), higher hospitalization cost ($14,223 vs $9,340, $P < .0001$), and lower readmission rates (24.8% vs 26.6%, $P = .0116$). However, in instrumental variables analysis, ONS use was associated with a 1.9-day (21.5%) decrease in LOS, from 8.8 to 6.9 days ($P < .01$); a hospitalization cost reduction of $1,570 (12.5%), from $12,523 to $10,953 ($P < .01$); and a 13.1% decrease in probability of 30-day readmission, from 0.34 to 0.29 ($P < .01$).

CONCLUSIONS: ONS may be associated with reduced LOS, hospitalization cost, and readmission risk in hospitalized Medicare patients with COPD. CHEST 2015; 147(6):1477-1484

Manuscript received June 6, 2014; revision accepted October 1, 2014; originally published Online First October 30, 2014.

ABBREVIATIONS: LOS = length of stay; ONS = oral nutritional supplementation

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This research has been presented previously at the 19th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), June 3, 2014, Montreal, QB, Canada; the 36th European Society for Clinical Nutrition and Metabolism (ESPEN) Congress, September 7, 2014, Geneva, Switzerland; and the 10th Congress of the European Union Geriatric Medicine Society (EUGMS), September 19, 2014, Rotterdam, The Netherlands.

FUNDING/SUPPORT: Support for this research was provided by Abbott Nutrition.

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COPD is a leading cause of morbidity and mortality, with 14.8 million prevalent diagnosed cases in the United States.[1] COPD is associated with progressive declines in respiratory function, mediated in part through frequent acute exacerbations as the disease worsens.[2,3] Declining respiratory function, in turn, leads to increased mortality risk,[4,5] reduced quality of life,[6-8] and greater risk of disability.[2,5,9,10]

COPD also imposes a substantial economic burden. In 2010, for example, the cost of COPD in the United States was estimated at nearly $50 billion annually.[2,11] Because of its typical onset later in life and its progressive nature,[2] COPD imposes particularly large costs on Medicare. Compared with age- and sex-matched counterparts without COPD, Medicare patients with COPD incurred approximately $20,500 (26.0%) more in healthcare costs in 2004.[12] In response to the growing prevalence of and large costs associated with COPD, Medicare is implementing new hospital quality targets designed specifically to measure and improve the quality of care provided to patients with COPD.[13] These targets include a mandate, beginning in 2015, to reduce preventable readmissions among patients with COPD. Under the mandate, hospitals with readmission rates above a risk-adjusted target will be required to pay penalties for the "excess" readmissions.[13,14] Given these quality initiatives and the fixed payments hospitals receive for the management of patients admitted with exacerbations of COPD, providers must find new, cost-effective strategies to improve the quality of hospital care for patients with COPD.

To date, much of the management of patients hospitalized with COPD has focused on the appropriate use of nebulized bronchodilators, systemic corticosteroids, supplemental oxygen, and antibiotics.[2,15,16] However, these management strategies neglect an important comorbidity of patients hospitalized with COPD: nutritional deficiency. Nutritional deficiency and negative energy balance are common among patients hospitalized with COPD, particularly during acute exacerbations,[17-19] and have been associated with poor prognoses.[20-22] Not surprisingly, growing evidence suggests that nutritional interventions such as vitamin D repletion,[23,24] dietary fiber,[25,26] and oral nutritional supplementation (ONS)[27-29] are associated with improved outcomes for patients with COPD on a variety of dimensions. In particular, ONS use is associated with improvements in weight gain, lean body mass, muscle strength, 6-min walking distance, and ability to exercise in patients with COPD.[28] Despite the importance of nutritional support in patients with COPD, however, current guidelines do not include specific recommendations for addressing nutritional deficiencies in this population.[16] Also, in addition to the clinical benefits to patients with COPD, nutritional support through ONS in other disease states has been associated with reduced costs,[30-34] length of stay (LOS),[27,35,36] and readmission rates among hospitalized patients.[35-37]

Despite the effects of nutritional deficiencies on morbidity and mortality in patients with COPD and the large burden of COPD-related costs to Medicare, limited evidence exists on the association between hospital use of ONS and outcomes of Medicare patients hospitalized with COPD. To address this issue, we examined the association between hospital ONS use and LOS, hospitalization cost, and 30-day readmission in Medicare patients aged ≥ 65 years hospitalized with COPD.

Materials and Methods

Data Source

The study sample was obtained from the Premier Research Database, which contains deidentified diagnostic information and billing records from 46 million hospitalizations in 460 hospitals from 2000 to 2010. Estimated to cover 20% of all US hospitalizations, the Premier database includes data from mostly small to midsized hospitals serving primarily urban populations in 41 states, representing all regions of the United States, and it is considered to be representative of US hospitalizations.[38]

Study Design

We focused on adults aged ≥ 65 years who were covered by Medicare and had a hospitalization with a primary diagnosis of COPD, as indicated by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 491.XX, 492.XX, and 496. Because our focus was on the association between ONS use and hospital outcomes, we excluded hospitalizations that involved tube feeding. Hospitalizations with either incomplete data or that resulted in in-hospital mortality were excluded. Our final sample included 378,419 hospitalizations.

Measures

We analyzed the association between hospital ONS use and three outcomes: LOS, hospitalization cost, and 30-day readmission. Hospitalization cost was defined as the cost of hospitalization rather than the amount reimbursed by Medicare. Costs included all supplies, labor costs, and depreciation of equipment. Monetary figures were reported in 2010 US dollars and were adjusted for inflation using the medical consumer price index from the Bureau of Labor Statistics.[27] A readmission was defined as a return hospitalization for any diagnosis occurring within 30 days of the original COPD hospitalization. For patient confidentiality purposes, the Premier database does not contain the exact discharge date, only the month and year, so the 30-day window was approximated by looking for admissions later in the same month or in the following month.

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DOI: 10.1378/chest.14-1368

The study treatment was defined as any ONS use during the inpatient hospitalization. Because there are no *International Classification of Diseases, Ninth Revision, Clinical Modification* or Current Procedural Terminology codes identifying ONS use, we relied on the Premier database definition of "complete nutritional supplement, oral." Product names given under this definition were manually checked for accuracy.

Covariates in our statistical analyses included age, age squared, insurance type (because some individuals had additional insurance beyond Medicare), marital status, race, sex, indicators of all comorbidities in the Charlson index,[5,39] history of admissions in the previous 6 months, and admission source (ED, physician referral, or interfacility transfer).

Statistical Analysis

Previous research has demonstrated that patients who receive ONS are, on average, more ill than those who do not receive ONS, not only on the basis of observed comorbidities but also on unobserved dimensions,[27] which leads to the possibility of selection bias. To address this potential bias, we used two techniques: propensity-score matching,[40] which controls for observed differences between individuals receiving ONS and those not receiving it, and instrumental variables analysis, which is an established approach in econometrics to account for both observed and unobserved differences.

To conduct the propensity-score matching, we used a logistic regression model to estimate the likelihood of receiving ONS as a function of the covariates noted previously. Each ONS hospitalization was matched to its nearest neighbor non-ONS hospitalization. Ordinary least squares regression analyses were then performed on the matched sample to determine the association between ONS use and the three study outcomes (LOS, hospitalization cost, and 30-day readmission), controlling for the covariates noted previously. To further control for patient heterogeneity in severity of illness, the model also included fixed effects for groups based on the duration of patient follow-up data: 1 day to 1 year, 1 to 2 years, 2 to 3 years, and >3 years. Because patient life expectancy could generally not be observed, follow-up duration served as a proxy for patient health status.

The propensity-score matching served to produce a sample that was more homogeneous in terms of observed characteristics such as age, sex, race, and comorbidities. Importantly, propensity score methods can help address confounding by observable characteristics by balancing the exposure and treatment groups according to those observable characteristics. Propensity score methods do not, however, address confounding in unobservable characteristics such as unmeasured health status and socioeconomic status, both of which may be associated with the propensity to receive ONS and hospital outcomes.

We, therefore, also performed an instrumental variables analysis on the matched sample. Instrumental variables analysis can help address bias from nonrandom selection into treatment by using an instrument that is correlated with treatment but otherwise unrelated to outcomes. For example, one of the first illustrations of instrumental variables analysis in a clinical context was a retrospective observational analysis of the association between more intensive treatments for acute myocardial infarction (namely, coronary revascularization vs thrombolysis) and mortality.[41] Since individuals at higher risk of mortality may be expected to receive more intensive treatments (thereby producing a positive correlation between the two variables), the study used differential distance to a percutaneous coronary intervention (PCI)-capable hospital as a source of randomization of patients to more vs less intensive treatment (ie, distance was an instrumental variable). The study demonstrated that patient distance to a PCI-capable site was strongly correlated with how intensively a patient with acute myocardial infarction was treated but uncorrelated with observed health status. Therefore, differential distance to PCI-capable sites was argued to effectively randomize patients to different propensities to receive intensive treatment. This analysis found evidence consistent with randomized controlled trials, namely intensive care was associated with improved mortality outcomes.

In the spirit of this illustration, we exploited the fact that there is significant variation across hospitals in the likelihood that patients receive ONS. We defined our instrument to be the fraction of hospitalizations in a given hospital in a given quarter involving any ONS use. Notably, this instrument was defined across all episodes in the hospital, not just those involving elderly Medicare patients with COPD, and, therefore, was unlikely to be related to the health status of the patients in this analysis. Details on instrument validation are presented in e-Appendix 1. Other research has relied on variations in provider practice patterns to identify causal effects of treatments.[42-44] Importantly, although instrumental variables analysis can help address confounding due to unmeasured covariates, it is not a substitute for randomized experimental study designs.

To facilitate comparison with the propensity-score matching model results, instrumental variables regression analyses were conducted using the same covariates as those used in the propensity-score analyses. (See e-Appendix 1 for comparison of these analyses.) In the case of cost analyses, regressions were performed on the natural logarithm of hospitalization cost to account for heteroskedastic errors. Results were then transformed back into dollars using Duan's smearing estimator.[45] Two-sided P values of $\leq 5\%$ were considered statistically significant.

Results

ONS was provided in 10,322 out of 378,419 hospitalizations (2.7%). Patients receiving ONS were, on average, 6 months older ($P<.0001$), more likely to have had a prior admission in the preceding 6 months (50.7% vs 41.2%, $P<.0001$), and less likely to be discharged to home (38.7% vs 59.4%, $P<.0001$) (Table 1). Hospitalizations in which ONS was provided were of longer duration (average LOS, 8.8 days vs 5.2 days, $P<.0001$) and higher cost ($14,405 vs $7,832, $P<.0001$) and were more likely to be followed by readmission (29.6% vs 25.3%, $P<.0001$).

Using propensity-score matching to match each ONS hospitalization to its nearest neighbor non-ONS hospitalization yielded a one-to-one matched sample of 14,326 hospitalizations. After matching, no statistically significant differences remained in the covariates. However, statistically significant differences remained in outcomes. For example, ONS use was associated with longer LOS (8.7 days vs 6.9 days, $P<.0001$) and higher hospitalization costs ($14,223 vs $9,340, $P<.0001$). ONS use was associated with lower readmission rates in the matched sample (24.8% vs 26.6%, $P=.0116$), although given their greater severity of illness, this may have been because a larger fraction of patients in ONS hospitalizations were lost to follow-up (eg, because of death or admission to a different facility). This possibility was taken into account in the readmission analyses described subsequently.

Instrumental variables analysis was used after covariate adjustment in the matched samples to address bias from

TABLE 1] Descriptive Statistics by ONS Use, Full and Matched Samples[a]

Characteristics	All COPD Hospitalizations			Matched COPD Hospitalizations		
	ONS (n = 10,322)	Non-ONS (n = 368,097)	*P* Value[b]	ONS (n = 7,163)	Non-ONS (n = 7,163)	*P* Value[b]
Age, mean (SD), y	76.7 (6.9)	76.2 (6.9)	<.0001	76.7 (6.9)	76.7 (6.9)	.8099
Sex						
Male	4,398 (42.6)	158,984 (43.2)	.4647	3,021 (42.2)	3,069 (42.9)	.4339
Female	5,924 (57.4)	209,108 (56.8)	…	4,142 (57.8)	4,093 (57.1)	…
Race						
White	8,265 (80.1)	279,032 (75.8)	<.0001	5,748 (80.3)	5,778 (80.7)	.2005
African American	583 (5.7)	25,514 (6.9)	…	406 (5.7)	406 (5.7)	…
Hispanic	284 (2.8)	10,683 (2.9)	…	209 (2.9)	240 (3.4)	…
Other	1,190 (11.5)	52,868 (14.4)	…	800 (11.2)	739 (10.3)	…
Length of stay, mean (SD), d	8.8 (8.0)	5.2 (5.8)	<.0001	8.7 (8.3)	6.9 (23.3)	<.0001
Hospitalization cost, mean (SD), $	14,405 (18,415)	7,832 (8,443)	<.0001	14,223 (18,914)	9,340 (15,078)	<.0001
Readmitted within 30 d	3,054 (29.6)	93,168 (25.3)	<.0001	1,774 (24.8)	1,906 (26.6)	.0116
Discharge to home	3,998 (38.7)	218,652 (59.4)	<.0001	2,850 (39.8)	3,580 (50.0)	<.0001
Admitted past 6 mo	5,234 (50.7)	151,611 (41.2)	<.0001	3,239 (45.2)	3,234 (45.2)	.9331
Admission from ED	7,258 (70.3)	271,241 (73.7)	<.0001	5,091 (71.1)	5,073 (70.8)	.7405
Charlson Index, mean (SD)	3.18 (2.4)	3.17 (2.2)	.8111	3.21 (2.4)	3.16 (2.4)	.2109
Charlson comorbidities						
Myocardial infarction	903 (8.8)	33,793 (9.2)	.1335	654 (9.1)	667 (9.3)	.7074
Congestive heart failure	3,281 (31.8)	112,341 (30.5)	.0058	2,349 (32.8)	2,377 (33.2)	.6188
Peripheral vascular disease	1,040 (10.1)	36,063 (9.8)	.3482	740 (10.3)	729 (10.2)	.7619
Cerebrovascular disease	582 (5.6)	14,949 (4.1)	<.0001	419 (5.9)	406 (5.7)	.6411
Dementia	430 (4.2)	11,097 (3.0)	<.0001	301 (4.2)	278 (3.9)	.3292
Connective tissue and rheumatic disease	276 (2.7)	10,110 (2.8)	.6559	182 (2.5)	183 (2.6)	.9577
Peptic ulcer disease	195 (1.9)	4,731 (1.3)	<.0001	137 (1.9)	149 (2.1)	.4735
Mild liver disease	152 (1.5)	3,746 (1.0)	<.0001	103 (1.4)	91 (1.3)	.3857
Diabetes without complications	1,872 (18.1)	89,003 (24.2)	<.0001	1,328 (18.5)	1,301 (18.2)	.5601
Diabetes with complications	179 (1.7)	8,283 (2.3)	.0005	131 (1.8)	115 (1.6)	.3035
Paraplegia and hemiplegia	43 (0.42)	899 (0.2)	.0005	26 (0.4)	25 (0.4)	.8884

(Continued)

TABLE 1 *(continued)*

Characteristics	All COPD Hospitalizations			Matched COPD Hospitalizations		
	ONS (n = 10,322)	Non-ONS (n = 368,097)	*P* Value[b]	ONS (n = 7,163)	Non-ONS (n = 7,163)	*P* Value[b]
Renal disease	808 (7.8)	35,900 (9.8)	< .0001	572 (8.0)	546 (7.6)	.4180
Cancer	832 (8.1)	19,672 (5.3)	< .0001	587 (8.2)	597 (8.3)	.7616
Moderate or severe liver cancer	27 (0.3)	420 (0.1)	< .0001	16 (0.2)	13 (0.2)	.5771
Metastatic cancer	265 (2.6)	5,285 (1.4)	< .0001	182 (2.5)	159 (2.2)	.2074
AIDS/HIV	4 (0.0)	88 (0.0)	.3400	4 (0.1)	4 (0.1)	1.0000

Data are shown as No. (%) unless otherwise indicated. ONS = oral nutritional supplementation.
[a]Sample excludes tube feeding. Definitions of "admitted past 6 mo" and "readmitted within 30 d" are approximate because the underlying data represents dates as month and year only.
[b]χ^2 test for categorical variables and Student *t* test for continuous variables.

selection on unobserved characteristics (Table 2). In this approach, ONS use was associated with a reduction in LOS of 21.5% (6.87 days vs 8.75 days, $P < .01$).

Similarly, ONS was associated with a reduction in hospitalization cost of $1,570, or 12.5% ($10,953 vs $12,523, $P < .01$). Given that the average cost to provide ONS was $88 per hospitalization[27] (including associated capital and labor expenses), this suggests that ONS use was cost effective, generating a reduction in hospital costs of nearly $18 for every $1 spent to provide ONS. In instrumental variables analysis of readmissions, ONS use was associated with a reduction in the 30-day readmission probability of 13.1% (0.291 vs 0.335, $P < .01$).

Discussion

Patients with COPD are at chronically high risk of nutritional deficiency,[21] which is deleterious to muscle, gut, and immune function.[46-48] Acute exacerbations are further complicated by impaired energy balance caused by reductions in dietary intake and increased resting metabolic energy expenditures.[17] Both facts suggest that nutritional support during periods of acute COPD exacerbation could have the potential to improve outcomes. Although ONS has been associated with improved outcomes among patients with COPD,[27,33,35-37] the role of hospital ONS in reducing LOS, cost, and readmission risk among hospitalized patients is unknown. Our study suggests that use of ONS among patients hospitalized with COPD is associated with reductions in LOS of 1.9 days (21.5%) ($P < .01$), reductions in hospitalization costs of $1,570 (12.5%) ($P < .01$), and reductions in 30-day readmission by 13.1% (from 0.335 to 0.291) ($P < .01$). These hypothesis-generating findings, if confirmed by randomized evidence, may stem from the ability of ONS to improve negative energy balance during periods of acute COPD exacerbation.[17-19]

In addition to the clinical benefits of lowered LOS and rehospitalization rates suggested by our study, our results have important policy implications given Medicare's current efforts to improve quality of care while restraining costs. In particular, our findings suggest the possibility that increased provision of ONS by hospitals could reduce costs of care for patients with COPD, while also decreasing their likelihood of being penalized for exceeding Medicare's new risk-adjusted readmission targets. Given that the total cost of ONS has been estimated at only $88 per hospitalization,[27] our estimated hospital cost reductions and the reduced risk of readmission penalties suggest that ONS may be highly cost effective.

TABLE 2] Effect of ONS Use on Hospital Episode-Level Outcomes

Outcome	Length of Stay	Episode Cost	Readmission Within 30 d, Probability
Effect of any ONS use	−1.88[a]	−1,570[a]	−0.0439[a]
SE	0.71	41.8	0.0162
Predicted outcome without ONS	8.75 d	$12,523	0.335
Predicted outcome with ONS	6.87 d	$10,953	0.291
Change caused by ONS use, %	−21.5	−12.5	−13.1
No. observations	14,326	14,326	11,712

Regression results from a matched sample of ONS hospitalizations matched 1:1 to non-ONS hospitalizations on propensity to receive ONS. Instrument is fraction of hospitalizations in a given hospital in a given quarter involving ONS use. For episode costs, dependent variable in the regressions is log of hospitalization cost. Costs are denominated in 2010 US dollars. Predicted hospitalization costs use Duan's smearing estimator. For readmission analysis, 30-d readmission window is approximate because only the month and year were observed in the data; readmission sample was restricted to those hospitalizations that could be tracked for follow-up. SEs take into account repeated observations of the same individual. See Table 1 for expansion of abbreviations.
[a]Significant at the 1% level.

Our findings are consistent with those of prior studies that suggest clinical benefit and reductions in healthcare costs associated with ONS use. Myint et al[34] found that ONS was associated with reductions in LOS of 3.8 days. Gariballa et al[35] found that ONS use was associated with reductions in readmissions by 27% in patients aged ≥ 65 years. Norman et al[36] and Cawood et al[49] also found that ONS use was associated with reduced readmissions. Assessing outcomes among adult inpatients in the Premier database, Philipson et al[27] found that ONS use was associated with reductions in LOS by 21.0%, hospital costs by 21.6%, and probability of readmission by 6.7%.

Nevertheless, existing evidence for the benefits of ONS in COPD is mixed. Until recently, meta-analyses and systematic reviews of the literature on nutritional supplementation found little evidence of benefit to patients with COPD.[50,51] A systematic review of randomized control trials of nutrition supplementation in COPD by Ferreira et al,[28] however, suggests increasing evidence that ONS use is associated with improved outcomes in patients with COPD, although their findings are mixed. These findings are based on 17 studies, with a total of 632 participants. Although we are unable to observe anthropometric data or clinical end points, our matched sample of 14,326 hospitalized patients with COPD makes this study the largest on this topic, to our knowledge.

Additionally, our study may be the first to assess the association between ONS use and hospital costs among patients with COPD in the United States. However, studies in other countries suggest ONS is cost effective.[30,32] In the United Kingdom, for example, the National Institute for Health and Clinical Excellence (NICE) concluded that ONS is valuable for malnourished patients and has issued guidelines recommending its use by physicians.[52]

Our study used an instrumental variables approach to attempt to address the fact that individuals receiving ONS are likely to be more ill on both observed and unobserved dimensions. The instrumental variables approach compared ONS hospitalizations to non-ONS hospitalizations in which the decision to provide ONS hinged on the provider's inclination to provide it, rather than on underlying patient characteristics. This creates a natural experiment, attempting to simulate randomization into treatment and control arms based on hospitals' propensity to provide ONS. The considerable difference in outcomes between unadjusted comparisions and instrumental variables analyses may reflect the extent of selection bias: After employing instrumental variables, the direction of the effect on every outcome was reversed (e-Appendix 1).

Our study has several limitations. First, although instrumental variable analysis can in theory address baseline differences in confounding variables, it cannot transform nonexperimental observational data into randomized trial evidence. We performed instrument validity tests that demonstrated that hospitals with high and low ONS use were not meaningfully different on many dimensions, which argues against unmeasured confounding. As with any instrumental variables analysis, however, we cannot rule out the possibility of confounding. For example, hospitals with high ONS rates may have malnutrition screening programs and may be more attuned to nutrition. If so, our estimated effects of ONS use may be construed as reflecting the impact of a bundle of hospital policies that promote nutritional support among acutely ill hospitalized patients. Therefore, our findings can only be viewed as tentative hypotheses that are suggestive of the possible effects of ONS use on hospital LOS, costs, and readmission rates.

Randomized trial evidence is needed to confirm these findings but may be difficult to obtain given ethical issues associated with withholding nutritional support from patients that are considered in need of this supplementation by providers.

A second limitation of our study is that the Premier data stem from hospital administrative records. It, therefore, does not contain clinical details such as laboratory test results and measures of nutritional status, which would be important to account for in our analysis.

In summary, our study suggests that ONS use is associated with reduced LOS, hospital costs, and readmission rates among patients with COPD. Screening for malnutrition among patients hospitalized with COPD and providing ONS to malnourished and nutritionally at-risk patients may offer significant health benefits to patients, as well as economic benefits to hospitals and the Medicare program. Randomized trial evidence is needed to confirm these hypotheses.

Conclusions

Our study suggests that use of ONS among Medicare patients hospitalized with COPD is associated with reduced LOS, hospitalization cost, and risk of 30-day readmission. ONS may offer an opportunity for hospitals to reduce costs and improve quality of care.

Acknowledgments

Author contributions: J. T. S. is the guarantor of the accuracy and completeness of the contents of this manuscript, including the data and analysis. J. T. S., M. T. L., R. A. H., J. S. P., C. L., and D. N. L. contributed to the conception and design of the research; J. T. S., A. B. J., M. T. L., R. A. H., J. S. P., C. L., D. N. L., and P. E. W. contributed to the analysis and interpretation of the data; J. T. S. and A. B. J. contributed to the drafting of the submitted article; and M. T. L., R. A. H., J. S. P., C. L., D. N. L., and P. E. W. contributed to critical revision of the manuscript for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Drs Snider, Jena, and Lakdawalla and Messrs Linthicum and LaVallee hold positions at Precision Health Economics, which receives consulting payments from Abbott Nutrition and other life sciences companies. Drs Hegazi and Partridge are employees of Abbott Nutrition, which provided funding for the study. Dr Wischmeyer has served as an occasional consultant and/or speaker for Abbott Nutrition, Baxter Healthcare Corp, Fresenius Medical Care, Nestlé, and Nutricia International over the past 3 years in the area of attempting to optimize clinical nutrition delivery. He receives research funding for nutrition work in illness and injury from the National Institutes of Health (R01 GM078312 and R34 HL109369), the US Department of Defense, the American Burn Association, and Fresenius Medical Care.

Role of sponsors: Abbott Nutrition provided input on the topic of the research and provided comments on the manuscript.

Other contributions: The authors thank Akua Boateng, MBS, MPH, and Jacquelyn Chou, MPP, MPL, of Precision Health Economics for research support.

Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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