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Impact of Socioeconomic Status on Pretreatment Weight Loss and Survival in Non–Small-Cell Lung Cancer

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QUESTION ASKED: Socioeconomic status (SES) influences health care outcomes in various settings including non–small-cell lung cancer (NSCLC), but what is the relationship between SES and pretreatment cancer-associated weight loss, and how does this influence treatment outcomes?

SUMMARY ANSWER: In a large cohort of > 1,300 adult patients with NSCLC, weight loss at the time of cancer diagnosis was common and associated with SES as measured by insurance status. In the absence of pretreatment weight loss, SES was not associated with survival; however, SES was significantly prognostic among patients with NSCLC with pretreatment weight loss.

WHAT WE DID: We performed a retrospective review of 1,366 adult patients with NSCLC consecutively treated at a tertiary care health system between January 1, 2006 and December 31, 2013. Cancer-associated weight loss was assessed using the validated international consensus definition of cancer cachexia.

WHAT WE FOUND: Pretreatment weight loss was observed in 30% of patients with NSCLC at the time of diagnosis including 17% with stage I disease. After controlling for other prognostic factors, Medicaid insurance (odds ratio, 2.17; 95% CI, 1.42 to 3.30) and lack of insurance (odds ratio, 2.32; 95% CI, 1.50 to 3.58) were independently associated with pretreatment weight loss. Among patients without pretreatment weight loss, insurance status was not prognostic of survival. In contrast, lack of insurance (hazard ratio, 1.63; 95% CI, 1.14 to 2.35) was significantly prognostic among patients with NSCLC with pretreatment weight loss. These findings highlight the potential impact of early recognition and management of cancer-associated weight loss in patients with NSCLC with lower SES in optimizing treatment outcomes.

BIAS, CONFOUNDING FACTOR(S), REAL-LIFE IMPLICATIONS: This study possesses the limitations inherent to all retrospective studies. Primary payer was used as the sole indicator of SES because educational attainment and household income on an individual patient level are not routinely documented at our institution. Generalization of these findings to malignancies other than NSCLC may be limited. JOP

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ASSOCIATED CONTENT

Appendix available online

Abstract

Purpose

Socioeconomic status (SES) influences health care outcomes, but the influence of primary payer on cancer-associated wasting is unknown. We hypothesized that primary payer as an indicator of SES would influence pretreatment cancer-associated weight loss and treatment outcomes.

Materials and Methods

Retrospective review of medical records identified 1,366 patients with non–small-cell lung cancer (NSCLC) consecutively treated at a tertiary care health system between January 1, 2006 and December 31, 2013. Insurance status was obtained from an institutional tumor registry. Cancer-associated weight loss was based on the validated international consensus definition of cachexia. Multivariable regression analyses were used to identify prognostic factors of pretreatment cancer-associated weight loss and survival.

Results

The cohort included a representative group of patients with a median age at diagnosis of 64 years, 47% females, and 33% patients of nonwhite race. Pretreatment cancer-associated weight loss was present at the time of NSCLC diagnosis in 17%, 14%, 32%, and 38% of patients with stage I, II, III, and IV disease, respectively. Pretreatment cancer-associated weight loss was associated with increasing age at diagnosis, black race, single marital status, tobacco use, and disease stage. Compared with private insurance, Medicaid insurance (odds ratio, 2.17; 95% CI, 1.42 to 3.30) and lack of insurance (odds ratio, 2.32; 95% CI, 1.50 to 3.58) were associated with pretreatment cancer-associated weight loss. Among cachectic patients, comorbidity, histology, tumor grade, and disease stage were prognostic of survival on multivariable analysis; however, primary payer was not.

Conclusion

Pretreatment cancer-associated weight loss is common in patients with NSCLC, and its presence is significantly associated with lower SES. However, among patients with pretreatment cancer-associated weight loss, SES was not predictive of survival. Early use of cancer cachexia–directed therapies may improve outcomes, and further study on the biologic mechanisms of cancer cachexia will provide novel therapeutic avenues.

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INTRODUCTION

Cancer cachexia is a multifactorial syndrome characterized by ongoing, unintentional weight loss that cannot be fully reversed by nutritional support and leads to progressive functional impairment.[1] Moreover, it is associated with decreases in tolerance to anticancer therapy, quality of life, and survival.[2-4] Importantly, weight loss occurring before the initiation of cancer therapies is also associated with these detrimental effects.[4] Therefore, identifying factors predictive of pretreatment cancer-associated weight loss is critical to providing optimal cancer therapy.

Socioeconomic status (SES) influences health care outcomes in various settings, including non–small-cell lung cancer (NSCLC).[5-9] Association of lower SES and diminished health outcomes has been proposed to be related to decreased access to medical care, which could further extend to anticachexia interventions.[5,6] However, the interaction of SES and cancer-associated weight loss is poorly described. To our knowledge, our report is the first to explore the impact of SES on pretreatment cancer-associated weight loss at the time of NSCLC diagnosis and the prognostic significance of SES in patients with cancer-associated weight loss.

MATERIALS AND METHODS

Population Cohort and Data Acquisition

Institutional review board approval was obtained for this study. A prospectively maintained institutional tumor registry identified 1,678 adult patients with a primary lung malignancy consecutively treated within a single tertiary care health system between January 1, 2006 and December 31, 2013. Patients with carcinoma in situ, small-cell lung cancer, carcinoid tumor, synchronous or metachronous malignancies, and incomplete electronic medical records were excluded. After these exclusions, 1,366 patients with NSCLC were eligible for further analysis. Patient and tumor characteristics were obtained from the registry. Primary payer was also obtained from the registry but was categorized as private insurance, Medicare, Medicaid, or uninsured (Appendix Fig A1, online only).

Assessment of Cancer-Associated Weight Loss

Medical records were systematically reviewed by a single author (B.S.G.) to assess for documented weight loss at the time of cancer diagnosis but before any therapeutic measure. Cancer-associated weight loss was defined using the well-accepted and validated international consensus definition of cachexia.[1] This is summarized as $>$ 5% weight loss over 6 months preceding the date of cancer diagnosis for patients with body mass index $\geq$ 20 kg/m^2 or unintentional weight loss $>$ 2% for patients with body mass index $<$ 20 kg/m^2. Patients with stable weight, weight gain, or purposeful weight loss were classified as not having weight loss. A second author (S.K.M.L.) independently reviewed the medical records of a random sample of patients and verified the results for these patients in a blinded manner.

Statistics

Inter-rater reliability was assessed using a κ coefficient. Descriptive statistics were used to summarize patient characteristics at baseline. Time to oncologist and time to therapy were compared using analysis of variance. Stepwise logistic regression was used to identify factors associated with the presence of cancer-associated weight loss at the time of cancer diagnosis. Stepwise Cox regression analysis was used to identify significant independent factors associated with overall survival among patients with weight loss. Factors with a P value $<$ .2 on univariable analysis were entered as variables in stepwise regression analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Population Cohort

A total of 1,366 adult patients with NSCLC were eligible for this study. Patient characteristics are presented in Table 1. The cohort was representative, with a median age at diagnosis of 64 years (range, 24 to 96 years), 725 (53.1%) men, and 449 (32.9%) patients of nonwhite race. The most common histology was adenocarcinoma (n = 742; 54.3%), with squamous cell carcinoma (n = 338; 24.7%) the second most common. Cancer-associated weight loss was present at the time of NSCLC diagnosis in 414 (30.3%) patients. Inter-rater κ coefficient was 0.71, indicating high concordance between raters.[10] A majority of patients had private or government-subsidized insurance: 522 (38.2%) patients had private insurance, 595 (43.6%) had Medicare, and 130 (9.5%) had Medicaid. In total, 112 (8.2%) patients were uninsured, and insurance status was unknown for only seven (0.5%) patients.

Delay to oncologist, defined as elapsed days from biopsy confirmation of malignancy to consultation with an oncology specialist, differed by insurance status ($P <$ .001). Patients with

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Characteristic	All (N=1,366)
Median age at diagnosis (IQR)	64 (56-72)
Male sex	725 (53.1)
Race	
White	917 (67.1)
Black	363 (26.6)
Other	67 (4.9)
Unknown	19 (1.4)
Ethnicity	
Hispanic	96 (7.0)
Non-Hispanic	1,248 (91.4)
Unknown	22 (1.6)
Marital status	
Single	380 (27.8)
Married	549 (40.2)
Divorced or separated	83 (6.1)
Widowed	159 (11.6)
Unknown	195 (14.3)
History of tobacco use	
Current	506 (37.0)
Prior	655 (48.0)
Never	181 (13.3)
Unknown	24 (1.8)
History of alcohol use	
Current	577 (42.2)
Prior	87 (6.4)
Never	586 (42.9)
Unknown	116 (8.5)
Charlson comorbidity score	
0	453 (33.2)
1	471 (34.5)
2	254 (18.6)
≥ 3	188 (13.8)
Pretreatment cachexia	
Present	414 (30.3)
Absent	952 (69.7)
Primary payer	
Private insurance	522 (38.2)
Medicare	595 (43.6)
Medicaid	130 (9.5)
Uninsured	112 (8.2)
Unknown	7 (0.5)
Median tumor size, mm (IQR)	35 (22-55)
NSCLC histology	
Adenocarcinoma	742 (54.3)
Squamous cell carcinoma	338 (24.7)
Other NSCLC	286 (20.9)
Grade	
I	54 (4.0)
II	299 (21.9)
III	357 (26.1)
IV	18 (1.3)
Unknown	638 (46.7)
Stage	
I	290 (21.2)
II	109 (8.0)
III	363 (26.6)
IV	604 (44.2)

NOTE. Data are presented as No. (%) unless otherwise noted.
Abbreviations: IQR, interquartile range; NSCLC, non–small-cell lung cancer.

private insurance had intermediate delay to oncologist (mean, 31 days), whereas patients with Medicare had significantly shorter delay to oncologist (mean, 24 days). Patients with Medicaid (mean, 37 days) and uninsured patients (mean, 48 days) had longer delays to oncologist. In contrast, delay to therapy, defined as elapsed days from biopsy to the first date of cancer-directed therapy, was similar regardless of insurance status ($P = .063$). Surgery and radiotherapy were used at similar rates by NSCLC stage, with the exception of surgery in stage III disease (20% of patients without pretreatment weight loss compared with 6% in its presence; $P < .001$).

Factors Associated With Pretreatment Weight Loss at NSCLC Diagnosis

Race, ethnicity, marital status, tobacco use, alcohol use, primary payer, Charlson comorbidity score, tumor stage, and tumor grade influenced pretreatment cancer-associated weight loss on univariable logistic regression. Age and histology did not influence pretreatment cancer-associated weight loss on univariable logistic regression (Table 2). Specifically, patients with Medicaid (odds ratio [OR], 2.84; 95% CI, 1.91 to 4.22) and the uninsured (OR, 2.82; 95% CI, 1.86 to 4.29) were more likely to have pretreatment weight loss. This was on a similar magnitude as black race compared with white race (OR, 1.91; 95% CI, 1.48 to 2.47) or stage IV disease

Table 2. Logistic Regression Identifying Factors Predictive of Pretreatment Cancer-Associated Weight Loss

	Univariable Analysis			Multivariable Analysis		
Variable	**Odds Ratio**	**95% CI**	***P***	**Odds Ratio**	**95% CI**	***P***
Age	0.99	(0.98 to 1.00)	.068	1.02	(1.00 to 1.03)	.038
Race						
White		Reference			Reference	
Black	1.91	(1.48 to 2.47)	< .001	1.56	(1.18 to 2.07)	.0019
Other	0.93	(0.53 to 1.65)	.81	0.81	(0.45 to 1.46)	.48
Unknown	0.51	(0.15 to 1.78)	.29	0.59	(0.16 to 2.09)	.41
Ethnicity						
Hispanic		Reference				
Non-Hispanic	0.64	(0.42 to 0.99)	.043			
Unknown	0.57	(0.21 to 1.59)	.29			
Marital status						
Single		Reference			Reference	
Married	0.51	(0.38 to 0.68)	< .001	0.64	(0.47 to 0.87)	.005
Divorced or separated	0.57	(0.34 to 0.98)	.043	0.66	(0.38 to 1.15)	.14
Widowed	0.59	(0.39 to 0.89)	.012	0.65	(0.42 to 1.00)	.0499
Unknown	1.28	(0.90 to 1.82)	.17	1.14	(0.78 to 1.66)	.50
Tobacco use						
Current		Reference				
Previous	0.62	(0.48 to 0.79)	< .001			
Never	0.45	(0.30 to 0.67)	< .001			
Unknown	0.55	(0.21 to 1.41)	.21			
Alcohol use						
Current		Reference				
Previous	1.60	(1.00 to 2.56)	.048			
Never	1.09	(0.85 to 1.40)	.51			
Unknown	1.17	(0.76 to 1.80)	.48			
Charlson comorbidity score						
0		Reference				
1	0.72	(0.54 to 0.95)	.021			
2	0.60	(0.42 to 0.84)	.0034			
≥ 3	0.89	(0.62 to 1.27)	.52			
Primary payer						
Private insurance		Reference			Reference	
Medicare	1.09	(0.83 to 1.42)	.55	1.03	(0.74 to 1.44)	.84
Medicaid	2.84	(1.91 to 4.22)	< .001	2.03	(1.33 to 3.11)	.0010
Uninsured	2.82	(1.86 to 4.29)	< .001	2.26	(1.46 to 3.50)	< .001
Unknown	0.49	(0.06 to 4.09)	.51	0.29	(0.03 to 2.47)	.25
Histology						
Adenocarcinoma		Reference				
Squamous cell carcinoma	1.21	(0.91 to 1.59)	.19			
Other NSCLC	1.19	(0.88 to 1.59)	.26			
Grade						
I		Reference				
II	2.27	(0.93 to 5.52)	.072			
III	3.66	(1.52 to 8.79)	.0038			

(continued on following page)

Table 2. Logistic Regression Identifying Factors Predictive of Pretreatment Cancer-Associated Weight Loss (continued)

	Univariable Analysis			Multivariable Analysis		
Variable	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
IV	6.40	(1.82 to 22.52)	.0039			
Unknown	4.27	(1.80 to 10.12)	.0010			
Stage						
I		Reference			Reference	
II	0.73	(0.39 to 1.36)	.32	0.70	(0.37 to 1.31)	.27
III	2.18	(1.50 to 3.16)	< .001	1.91	(1.29 to 2.81)	.0011
IV	2.82	(2.00 to 3.96)	< .001	2.52	(1.75 to 3.62)	< .001

Abbreviation: NSCLC, non–small-cell lung cancer.

compared with stage I disease (OR, 2.82; 95% CI, 2.00 to 3.98). Married and widower statuses were protective for pretreatment weight loss. (OR, 0.51; 95% CI, 0.38 to 0.68).

Stepwise multivariable logistic regression was used to further identify factors independently associated with pretreatment wasting (Table 2). Increasing age and tumor stage were positively correlated with pretreatment weight loss at NSCLC diagnosis, as was black race. Married status was protective for pretreatment weight loss. After accounting for other factors, primary payer remained an independent predictor of pretreatment cancer-associated weight loss. Compared with patients with private insurance, those with Medicaid (OR, 2.03; 95% CI, 1.33 to 3.11) and the uninsured (OR, 2.26; 95% CI, 1.46 to 3.50) were more likely to have pretreatment weight loss.

Factors Associated With Survival in Patients With NSCLC With Weight Loss

Median survival for all patients was 17.0 months. Cox regression analysis was performed to test the hypothesis that lower SES is associated with worse survival for patients with cancer-associated weight loss. Among the 414 patients with pretreatment weight loss at NSCLC diagnosis, patient age, marital status, Charlson comorbidity score, primary payer, tumor histology, tumor grade, and tumor stage were associated with survival on univariable Cox regression (Table 3). Specifically, divorced or legally separated (hazard ratio [HR], 0.41; 95% CI, 0.21 to 0.78) and widowed marital status (HR, 0.63; 95% CI, 0.41 to 0.98) were associated with increased survival compared with single status. There was a paradoxical association of Charlson comorbidity score 2 with survival compared with patients with a score of 0 (HR, 0.68; 95% CI, 0.48 to 0.98). Among patients with pretreatment weight loss, uninsured patients had diminished survival compared with those with private insurance (HR, 1.63; 95% CI, 1.14 to 2.35). Insurance status was not associated with survival for patients without pretreatment weight loss (data not shown). Race, ethnicity, tobacco use, and alcohol use were not prognostic of survival on univariable analysis.

Stepwise multivariable Cox regression was used to further identify predictors of overall survival among patients with NSCLC with pretreatment weight loss (Table 3). As expected, increased tumor stage was prognostic of diminished survival. Squamous cell (HR, 1.61; 95% CI, 1.20 to 2.16) and other NSCLC histology (HR, 1.65; 95% CI, 1.22 to 2.22) were also associated with worse survival compared with adenocarcinoma. SES as represented by primary payer was not independently prognostic of survival on multivariable analysis for patients with NSCLC with pretreatment weight loss.

DISCUSSION

SES is prognostic of various health care outcomes, and the association of lower SES with worse outcomes has been attributed to diminished access to medical care.[5-7] Cancer cachexia is clearly associated with functional impairment and poor prognosis.[2,3] Moreover, weight loss occurring before any cancer therapy is prognostic of diminished survival for patients with advanced NSCLC.[4] However, the influence of SES on cancer cachexia is unknown. To our knowledge, this study is the first to assess the impact of SES on pretreatment cancer-associated weight loss and survival among cachectic patients with NSCLC. For the first time, we demonstrate primary payer as an independent predictor of pretreatment cancer-associated weight loss in a diverse cohort of patients with NSCLC (Table 2). Interestingly, among patients with weight loss at the time of cancer diagnosis, SES as measured by

Table 3. Cox Regression Identifying Factors Prognostic for Survival Among Patients With Pretreatment Cancer-Associated Weight Loss

	Univariable Analysis			Multivariable Analysis		
Variable	**Hazard Ratio**	**95% CI**	***P***	**Hazard Ratio**	**95% CI**	***P***
Age	0.99	(0.98 to 1.00)	.013			
Race						
White		Reference				
Black	1.08	(0.84 to 1.37)	.56			
Other	1.21	(0.70 to 2.09)	.50			
Unknown	1.68	(0.54 to 5.29)	.37			
Ethnicity						
Hispanic		Reference				
Non-Hispanic	0.85	(0.56 to 1.27)	.41			
Unknown	1.28	(0.53 to 3.11)	.59			
Marital status						
Single		Reference				
Married	0.85	(0.64 to 1.13)	.25			
Divorced or separated	0.41	(0.21 to 0.78)	.007			
Widowed	0.63	(0.41 to 0.98)	.042			
Unknown	1.25	(0.92 to 1.68)	.16			
Tobacco use						
Current		Reference				
Previous	0.82	(0.65 to 1.05)	.11			
Never	0.81	(0.54 to 1.22)	.31			
Unknown	0.90	(0.37 to 2.19)	.81			
Alcohol use						
Current		Reference				
Previous	0.87	(0.56 to 1.34)	.51			
Never	0.91	(0.71 to 1.17)	.48			
Unknown	1.11	(0.75 to 1.64)	.61			
Charlson comorbidity score						
0		Reference			Reference	
1	1.14	(0.88 to 1.49)	.32	1.12	(0.86 to 1.47)	.39
2	0.68	(0.48 to 0.98)	.038	0.68	(0.47 to 0.98)	.039
≥ 3	0.57	(0.39 to 0.83)	.0034	0.80	(0.54 to 1.18)	.26
Primary payer						
Private insurance		Reference				
Medicare	0.98	(0.75 to 1.29)	.88			
Medicaid	1.34	(0.94 to 1.90)	.11			
Uninsured	1.63	(1.14 to 2.35)	.0079			
Histology						
Adenocarcinoma		Reference			Reference	
Squamous cell carcinoma	1.14	(0.86 to 1.49)	.36	1.61	(1.20 to 2.16)	.0015
Other NSCLC	1.47	(1.11 to 1.95)	.0067	1.65	(1.22 to 2.22)	.0010
Grade						
I		Reference			Reference	
II	1.02	(0.31 to 3.30)	.98	0.92	(0.28 to 3.03)	.90
III	1.75	(0.55 to 5.56)	.34	1.46	(0.45 to 4.70)	.53

(continued on following page)

Table 3. Cox Regression Identifying Factors Prognostic for Survival Among Patients With Pretreatment Cancer-Associated Weight Loss (continued)

	Univariable Analysis			Multivariable Analysis		
Variable	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
IV	3.51	(0.91 to 13.58)	.069	2.81	(0.71 to 11.16)	.14
Unknown	2.12	(0.68 to 6.65)	.20	1.44	(0.46 to 4.57)	.53
Stage						
I		Reference			Reference	
II	0.85	(0.37 to 1.95)	.69	0.60	(0.26 to 1.42)	.25
III	1.99	(1.27 to 3.11)	.0026	1.63	(1.02 to 2.59)	.040
IV	4.12	(2.72 to 6.26)	< .001	4.00	(2.58 to 6.20)	< .001

Abbreviation: NSCLC, non–small-cell lung cancer.

primary payer was not independently prognostic of survival (Table 3).

The association of primary payer with pretreatment cancer-associated weight loss in our cohort is provocative. Prior studies have focused on an association of lower SES with more advanced malignancy at the time of diagnosis.[8,9] Halpern et al[8] reviewed > 3.7 million patients, including 693,697 patients with lung cancer, registered to the National Cancer Database. Medicaid insurance and lack of insurance were associated with more advanced stage at presentation compared with private insurance.[8] Lower SES was also correlated with more advanced NSCLC stage at diagnosis in our cohort (data not shown). Interestingly, primary payer remained predictive of pretreatment cancer-associated weight loss after controlling for stage. Together, these findings suggest SES influences multiple aspects of oncogenesis and disease presentation.

Although lower SES was prognostic for survival when all patients in our cohort were included (data not shown), SES as represented by primary payer was not independently prognostic among patients with pretreatment weight loss. Previous studies have revealed an association of lower SES with diminished survival.[5,6,11,12] Cella et al[5] reviewed 2,089 patients, including 961 patients with lung cancer, enrolled in eight Cancer and Leukemia Group B protocols. Lower income and lower educational attainment were prognostic of worse survival even after controlling for stage at presentation.[5] Interestingly, SES remains a powerful prognostic indicator of cancer survival in universal health care systems designed with equal access in mind.[13,14] Together, these findings suggest pretreatment cancer-associated weight loss has a stronger influence on survival than SES. A complementary possibility is that currently available anticachexia therapies, which may be more readily available to patients of higher SES, do not provide durable benefit or are not used early enough before patients progress to refractory cachexia.[15]

Among those with pretreatment weight loss, the paradoxical association of Charlson comorbidity score 2 with overall survival has several possible explanations. The group may be heterogeneous, because comorbidities of varying severity may lead to a Charlson score of 2. Similarly, the increasing early diagnosis of comorbid conditions, such as diabetes mellitus, may alter the prognostic significance of them. Finally, could a comorbidity or its treatments, such as diabetes and metformin, actually be protective against the negative prognostic effects of weight loss? This raises interesting points that will be further explored.

This analysis has limitations inherent to all retrospective studies. Although patients were identified using a prospectively maintained database, the presence of cancer-associated weight loss was retrospectively assessed. Although cancer-associated weight loss was based on the consensus definition of cachexia, the diagnostic criterion of sarcopenia was omitted because muscle mass measurements are not routinely performed at our institution.[1] Moreover, primary payer was the sole indicator of SES because educational attainment and household income on an individual patient level are not routinely documented at our institution. Finally, because all patients in our cohort had NSCLC, the generalization of these findings to malignancies other than NSCLC may be limited.

In conclusion, patients with NSCLC of lower SES as measured by primary payer are disproportionately affected by cancer-associated weight loss, which in turn is prognostic of diminished survival. Among patients with pretreatment weight loss, lower SES is not independently prognostic of survival. These findings suggest early recognition and management

of cachexia, even at the time of cancer diagnosis, could result in improved survival. JOP

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Authors' Disclosures of Potential Conflicts of Interest

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

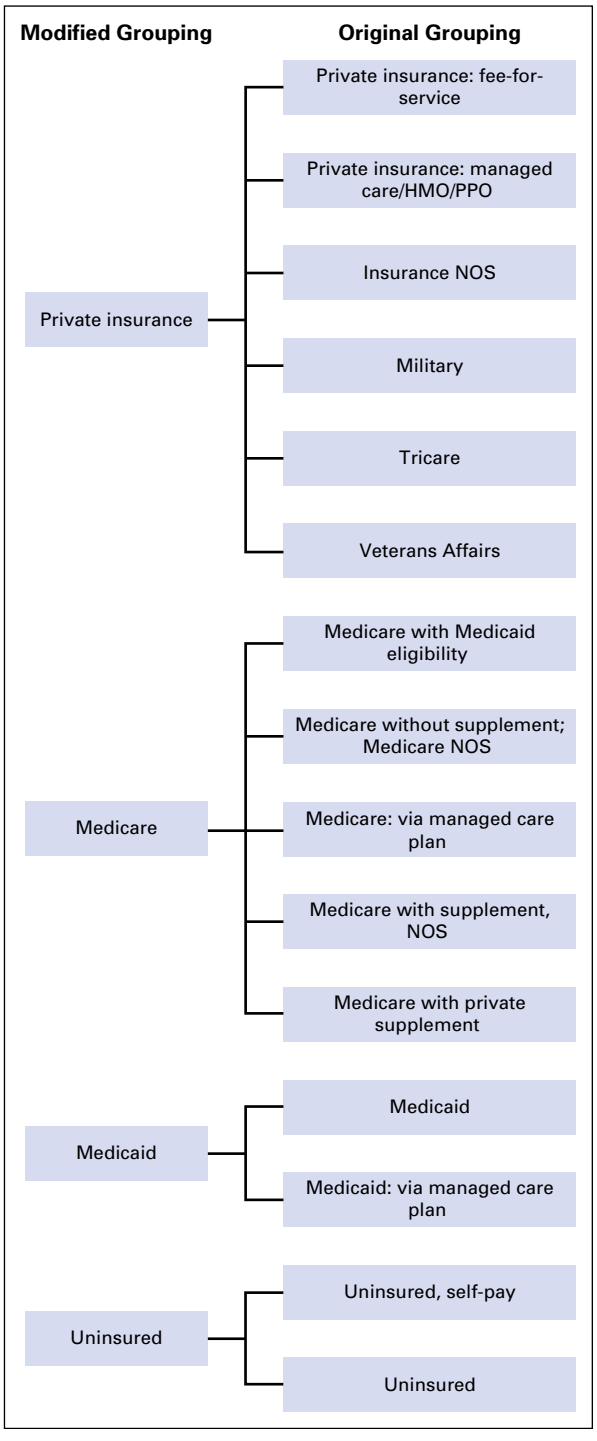

Fig A1. Classification schema for insurance status. HMO, health maintenance organization; NOS, not otherwise specified; PPO, preferred provider organization.