Carcinoid Syndrome and Costs of Care During the First Year After Diagnosis of Neuroendocrine Tumors Among Elderly Patients

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Neuroendocrine tumors (NETs) can secrete hormonal peptides that lead to additional symptom burdens. However, it is largely unknown whether and to what extent the additional symptom burdens translate into higher costs of care. This study aimed to examine the cost pattern of elderly NET patients during the first year of diagnosis, taking into account of the carcinoid syndrome status.

Methods. We used Surveillance, Epidemiology, and End Results Medicare data to identify elderly NET patients diagnosed between January 2003 and December 2011. Patients who had at least two claims indicative of carcinoid syndrome during the 3 months before and after the NET diagnosis were considered to have carcinoid syndrome. We adopted a payer's perspective and quantified economic outcomes using the following three measures: (a) total Medicare reimbursement amount, (b) inpatient amount,

and (c) outpatient amount. We used a generalized linear model (GLM) to examine the association between syndrome and costs.

Results. Our study cohort included 6,749 elderly NET well-differentiated and moderately differentiated patients. Of these patients, 5,633 (83%) were alive 1 year after diagnosis with continuous enrollment, and 1,116 (17%) died within 1 year. The multivariable GLM showed significant association between the syndrome and higher total, inpatient, and outpatient costs among the group who survived the whole year; the association was insignificant among the group who died within the first year of diagnosis.

Conclusion. This population-based study showed that NET patients with carcinoid syndrome incurred higher costs of care especially among those who survived the first year of diagnosis. *The Oncologist* 2017;22:1451–1462

Implications for Practice: This is the first population-based study that examines the health care costs associated with carcinoid syndrome among neuroendocrine tumor patients. Among patients alive throughout the first year, the unadjusted analyses showed that total median monthly costs were above $1,000 higher ($3,801 vs. $2,481) for patients with carcinoid syndrome compared with patients without. A significant association was found between carcinoid syndrome and higher total inpatient and outpatient costs among the group that survived the whole year even after controlling for clinical factors, treatment received, and demographics and neighborhood socioeconomic status; the association was insignificant among the group that died within the first year of diagnosis.

Introduction

Neuroendocrine tumors (NETs) start from the hormone-producing cells of the human body's neuroendocrine system. They can be found throughout the body and are usually categorized based on either their anatomic location or their embryonic origin. The incidence of NETs has been steadily increasing. The annual age-adjusted incidence of NETs increased more than fivefold from 1973 (1.09/100,000) to 2004 (5.25/100,000) [1]. A more recent study [2, 3] showed that the incidence is continuing to increase, possibly due to advances in diagnostic techniques such as computerized tomography and endoscopy and higher awareness among clinicians. Meanwhile, the

prevalence is increasing even more substantially because the survival of NET patients has improved significantly over time. Such better survival rates of NET patients may have resulted from more patients being diagnosed at an early stage and lower grade, and also from evolution of systemic therapies for distant stage patients.

NETs can secrete hormonal peptides that lead to a condition known as carcinoid syndrome [4]. Patients with carcinoid syndrome bear additional symptom burdens such as flushing, diarrhea, wheezing, and fibrotic valvular heart disease [5]. The current recommended treatment for hormone secretion and

associated symptoms involves the use of somatostatin analogues, which can reduce, but not eliminate, the symptom burden among the majority of patients [6–8]. Given the increasing survival and prevalence of NETs, a large number of patients suffer the symptom burden of carcinoid syndrome. However, it is largely unknown whether and to what extent the additional symptom burdens translate into higher costs of care. This study aims to examine the cost pattern of elderly NET patients during the first year of diagnosis, taking into account the presence of carcinoid syndrome.

MATERIALS AND METHODS

Data Source

We used the Surveillance, Epidemiology, and End Results (SEER) registry data linked with Medicare claims for this study. The SEER program of the National Cancer Institute collects incidence and survival data on all cancers in 18 selected geographic areas and covered approximately 30% of the U.S. population [9]. The SEER registry data includes information on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. Offering linkage to Medicare claims data, the SEER-Medicare data provides additional information on enrollment to Medicare plans, the utilization of health care resources, comorbidities, and other patient information such as neighborhood socioeconomic status (SES). The SEER-Medicare database is a widely used data source for the study of health care resource utilizations in oncology and is considered to be representative of the U.S. elderly population [10].

Study Cohort

We first selected patients diagnosed with NETs between January 1, 2003, and December 31, 2011, based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes: 8240, 8241, 8242, 8243, 8244, 8245, 8246, and 8249 (gastrointestinal and pulmonary carcinoids and neuroendocrine carcinomas). Then we excluded patients with pancreas as their primary tumor site because while pancreatic NETs may secrete hormones that cause secretory syndromes, they may not produce the typical carcinoid syndrome. We also excluded patients with stage in situ and patients less than 65 years old at the time of diagnosis. Further, we required that the patients have continuous Medicare Parts A and B enrollment and no Health Management Organization (HMO) enrollment during the 12 months before and the 12 months after the NET diagnosis to ensure the completeness of medical claims used to capture patient comorbidities and utilization of health care services, respectively, because when patients are enrolled in HMOs, we do not have detailed claims information to capture their utilization of health care services. Patients with poorly differentiated neuroendocrine carcinomas and neuroendocrine neoplasms of unspecified grade were excluded to provide a homogeneous population of patients. The final study cohort included 6,749 patients with well-differentiated and moderately differentiated tumors. Supplemental online Fig. 1 is a detailed flowchart for the inclusion and exclusion criteria of our study cohort.

Costs of Care

We adopted a payer's perspective and examined costs of care based on Medicare payment amount. We examined three types of costs: (a) total costs, (b) inpatients costs, and (c) outpatient costs. We studied the average monthly Medicare payment amount normalized to the first half of 2016 dollars based on the medical care services consumer price index [11].

Key Explanatory Variable: Presence of Carcinoid Syndrome

We identified patients with carcinoid syndrome based on the following International Classification of Disease 9th Revision (ICD-9) codes: flushing (782.62), diarrhea (564.5, 787.91), and carcinoid syndrome (259.2). As in prior analyses [12, 13], patients who had at least two claims with any of the above mentioned ICD-9 codes during a 6 month time window between 3 months before and 3 months after the NET diagnosis were considered to have carcinoid syndrome.

Other Explanatory Variables

We included clinical factors, treatment received, patient demographics, comorbidities, and neighborhood SES in our analyses. The clinical factors included stage of the tumor (local/regional, distant, and unknown), histological grade (well-differentiated, moderately differentiated), tumor site (larynx, bronchus, lung, trachea and other respiratory organs; cecum and appendix; colon; small intestine; and all others). We included the following four indicators for treatment received: (a) chemotherapy (yes/no), (b) radiotherapy (yes/no), (c) resection of primary tumors (yes/no), and (d) resection of liver metastasis (yes/no). Patient demographics included age (65–69, 70–74, 75–79, ≥80), gender (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics or all others), region (Northeast, West, Midwest, South), and urban/rural status (metropolitan vs. nonmetropolitan). We used the Deyo-Romano modified Charlson comorbidity score [14–16] categorized into four groups: (a) zero, (b) one, (c) two, and (d) at least three. We also considered neighborhood SES based on three measures in terms of the following quartiles: (a) percent with at least high school education, (b) median household income, and (c) percent living in poverty.

Statistical Analysis

We provided the descriptive statistics for the study sample by whether the patients survived throughout the first year of diagnosis. We conducted separate analyses for patients who were alive throughout the year after diagnosis and patients who died within a year because these patients have very different cost patterns due to the high cost of terminal care. We compared the group difference by the presence of carcinoid syndrome using chi-square statistics. For comparison of costs, we used the Wilcoxon-Mann-Whitney test; for the occurrence of emergency room (ER) admissions and hospitalizations, we used the chi-square test.

We used a generalized linear model (GLM) with log link function and gamma distribution for the multivariable regression analyses of costs. The estimated impact in term of dollars, the 95% confidence interval, and p values are presented. As explained above, we separately analyzed the cost pattern of patients who survived the whole first year after diagnosis and patients who died within a year.

Table 1. Description of the study sample by vital status and whether carcinoid syndrome was observed

Covariates	Alive throughout the first year			Dead within the first year		
	With syndrome	Without syndrome	p value	With syndrome	Without syndrome	p value
All, n (%)	1,189 (21.11%)	4,444 (78.89%)		296 (26.52%)	820 (73.48%)	
Demographic and clinical factors						
Age, n (%)			.227			.93
<70	315 (21.65%)	1,140 (78.35%)		40 (27.78%)	104 (72.22%)	
70–74	310 (20.21%)	1,224 (79.79%)		61 (27.11%)	164 (72.89%)	
75–79	259 (19.88%)	1,044 (80.12%)		68 (25.09%)	203 (74.91%)	
≥80	305 (22.74%)	1,036 (77.26%)		127 (26.68%)	349 (73.32%)	
Gender, n (%)			.703			.003
Male	481 (20.86%)	1,825 (79.14%)		116 (22.35%)	403 (77.65%)	
Female	708 (21.28%)	2,619 (78.72%)		180 (30.15%)	417 (69.85%)	
Race, n (%)			<.001			.032
Non-Hispanic white	997 (22.42%)	3,450 (77.58%)		249 (28.33%)	630 (71.67%)	
Non-Hispanic black	99 (16.50%)	501 (83.50%)		27 (19.85%)	109 (80.15%)	
Hispanic or others	93 (15.87%)	493 (84.13%)		20 (19.80%)	81 (80.20%)	
Histologic stage, n (%)			<.001			<.001
Localized	381 (11.90%)	2,822 (88.10%)		65 (16.09%)	339 (83.91%)	
Regional	337 (32.16%)	711 (67.84%)		49 (25.26%)	145 (74.74%)	
Distant	290 (43.41%)	378 (56.59%)		94 (34.56%)	178 (65.44%)	
Unstaged or unknown	181 (25.35%)	533 (74.65%)		88 (35.77%)	158 (64.23%)	
Grade, n (%)			.015			.015
Well-differentiated	1,092 (21.55%)	3975 (78.45%)		265 (27.87%)	686 (72.13%)	
Moderately differentiated	97 (17.14%)	469 (82.86%)		31 (18.79%)	134 (81.21%)	
Census tract % below poverty level in quartile, n (%)			.025			.099
1st quartile	293 (20.75%)	1,119 (79.25%)		72 (29.75%)	170 (70.25%)	
2nd quartile	343 (23.87%)	1,094 (76.13%)		75 (26.13%)	212 (73.87%)	
3rd quartile	276 (19.71%)	1,124 (80.29%)		83 (29.43%)	199 (70.57%)	
4th quartile	277 (20.01%)	1,107 (79.99%)		66 (21.64%)	239 (78.36%)	
Census tract median income in quartile, n (%)			.088			.416
1st quartile	284 (19.57%)	1,167 (80.43%)		81 (25.00%)	243 (75.00%)	
2nd quartile	284 (20.13%)	1,127 (79.87%)		74 (25.00%)	222 (75.00%)	
3rd quartile	300 (21.69%)	1,083 (78.31%)		70 (26.42%)	195 (73.58%)	
4th quartile	321 (23.13%)	1,067 (76.87%)		71 (30.74%)	160 (69.26%)	
Census tract % with at least high school diploma education in quartile, n (%)			.847			.476
1st quartile	290 (20.60%)	1,118 (79.40%)		69 (23.79%)	221 (76.21%)	
2nd quartile	298 (21.61%)	1,081 (78.39%)		82 (27.15%)	220 (72.85%)	
3rd quartile	307 (21.59%)	1,115 (78.41%)		83 (29.43%)	199 (70.57%)	
4th quartile	294 (20.65%)	1,130 (79.35%)		62 (25.62%)	180 (74.38%)	
Comorbidity score, n (%)			.142			.003
0	593 (22.45%)	2,049 (77.55%)		108 (33.54%)	214 (66.46%)	
1	307 (19.72%)	1,250 (80.28%)		74 (26.91%)	201 (73.09%)	
2	144 (20.25%)	567 (79.75%)		37 (20.90%)	140 (79.10%)	
≥3	145 (20.06%)	578 (79.94%)		77 (22.51%)	265 (77.49%)	
Region, n (%)			.093			.182
Midwest	146 (18.67%)	636 (81.33%)		40 (23.39%)	131 (76.61%)	
Northeast	247 (21.24%)	916 (78.76%)		58 (29.59%)	138 (70.41%)	

(continued)

Table 1. (continued)

Covariates	Alive throughout the first year			Dead within the first year		
	With syndrome	Without syndrome	*p* value	With syndrome	Without syndrome	*p* value
South	291 (20.11%)	1,156 (79.89%)		91 (29.84%)	214 (70.16%)	
West	505 (22.53%)	1,736 (77.47%)		107 (24.10%)	337 (75.90%)	
Site, n (%)			< .001			< .001
Cecum and appendix	75 (36.76%)	129 (63.24%)		18 (40.00%)	27 (60.00%)	
Colon	102 (10.79%)	843 (89.21%)		22 (23.16%)	73 (76.84%)	
Larynx, bronchus,	149 (9.55%)	1,412 (90.45%)		31 (12.02%)	227 (87.98%)	
Others	248 (24.48%)	765 (75.52%)		124 (40.52%)	182 (59.48%)	
Small intestine	614 (32.28%)	1,288 (67.72%)		101 (24.75%)	307 (75.25%)	
Urban/rural status, n (%)			.138			.806
Metropolitan	1,011 (21.46%)	3,699 (78.54%)		248 (26.38%)	692 (73.62%)	
Nonmetropolitan	178 (19.28%)	745 (80.72%)		48 (27.27%)	128 (72.73%)	
Chemotherapy, n (%)			< .001			.246
Yes	212 (34.87%)	396 (65.13%)		49 (30.25%)	113 (69.75%)	
No	977 (19.44%)	4,048 (80.56%)		247 (25.89%)	707 (74.11%)	
Radiotherapy, n (%)			.149			.074
Yes	53 (17.79%)	245 (82.21%)		19 (19.00%)	81 (81.00%)	
No	1,136 (21.29%)	4199 (78.71%)		277 (27.26%)	739 (72.74%)	
Resection of liver metastasis, n (%)			< .001			.591
Yes	50 (50.51%)	49 (49.49%)		Masked[a]	Masked[a]	
No	1,139 (20.58%)	4395 (79.42%)		292 (26.45%)	812 (73.55%)	
Resection of primary tumors, n (%)			.005			.045
Yes	819 (20.16%)	3,244 (79.84%)		120 (23.62%)	388 (76.38%)	
No	370 (23.57%)	1200 (76.43%)		176 (28.95%)	432 (71.05%)	
Total monthly costs			< .0001			.411
Mean (SD)	4,658.18 (3,730.74)	3,170.32 (3,254.10)		17,427.40 (16,658.5)	18,058.28 (18,760.7)	
Median	3801.85	2481.17		13,164.34	12392.73	
Outpatient monthly costs			< .0001			.0002
Mean (SD)	1,834.62 (1,768.50)	1,041.62 (1,174.87)		2,430.34 (2,538.51)	2,100.98 (2,531.48)	
Median	1,150.93	678.63		1,966.77	1258.73	
Inpatient monthly costs			< .0001			.6064
Mean (SD)	2,823.56 (3,058.87)	2,128.70 (2,759.83)		14,997.06 (17,165.3)	15,957.30 (19,348.3)	
Median	2,254.41	1625.35		10,665.19	10030.16	
Any ER admissions, n (%)			< .001			.068
Yes	496 (26.78%)	1356 (73.22%)		201 (28.35%)	508 (71.65%)	
No	693 (18.33%)	3088 (81.67%)		95 (23.34%)	312 (76.66%)	
Any hospitalizations, n (%)			< .001			.007
Yes	947 (23.39%)	3102 (76.61%)		263 (28.10%)	673 (71.90%)	
No	242 (15.28%)	1342 (84.72%)		33 (18.33%)	147 (81.67%)	

[a]Masked per Surveillance, Epidemiology, and End Results-Medicare user agreement for confidentiality.

To examine the time trend of incurred cost during the year, we provided figures showing the total, inpatient, and outpatient costs incurred in each month after diagnosis for the following five groups of NET patients: (a) patients who were alive throughout the whole year, (b) patients who died within 3 months, (c) patients who died within 6 months, (d) patients who died within 9 months, and (e) patients who died within 12 months.

All statistical analyses were conducted in SAS Enterprise Guide 6.1 (analytical software; SAS Institute, Cary, NC, http://www.sas.com). The Institutional Review Board at The University of Texas MD Anderson Cancer Center exempted this study for

Table 2. Multivariate Regression Analysis for the cohort alive throughout the first year

	Overall incremental monthly costs compared to reference			Incremental inpatient monthly costs compared to reference			Incremental outpatient monthly costs compared to reference		
	Estimate ($)	CI	p value	Estimate ($)	CI	p value	Estimate ($)	CI	p value
Carcinoid syndrome									
Yes	504.9	(324, 749)	<.001	187.9	(58, 371)	.002	293.8	(211, 401)	<.001
No (reference)									
Age									
65–69 (reference)									
70–74	110.8	(4, 264)	.04	9.68	(−95, 164)	.879	46.39	(9, 99)	.012
75–79	92.69	(−14, 248)	.099	41.61	(−73, 211)	.535	32.01	(−5, 84)	.094
≥80	256.7	(116, 455)	<.001	207.4	(59, 419)	.003	17.22	(−17, 65)	.363
Gender									
Female (reference)									
Male	75.38	(−3, 187)	.063	100.8	(4, 239)	.041	7.84	(−16, 41)	.563
Race									
Non-Hispanic white (reference)									
Non-Hispanic black	228.9	(73, 452)	.001	432.5	(207, 752)	<.001	68.75	(18, 140)	.004
Hispanic or Others	−239	(−293, −144)	<.001	45.98	(−109, 281)	.619	−59.1	(−84, −20)	.006
Comorbidity score									
0 (reference)									
1	296.2	(164, 478)	<.001	258.9	(118, 455)	<.001	100.9	(57, 160)	<.001
2	593.5	(372, 897)	<.001	528.5	(303, 841)	<.001	189.5	(119, 284)	<.001
≥3	1,359	(967, 1881)	<.001	1,058	(716, 1518)	<.001	441	(319, 601)	<.001
Site									
Larynx, bronchus, lung, trachea, and other (reference)									
Cecum and appendix	77.5	(−108, 368)	.478	136.8	(−78, 465)	.253	−33.4	(−83, 44)	.345
Colon	−767	(−702, −827)	<.001	−268	(−349, −131)	.001	−91.1	(−107, −63)	<.001
Others	−132	(−205, −15)	.031	−27.4	(−149, 157)	.729	133	(72, 216)	<.001
Small intestine	58.94	(−37, 199)	.267	243.3	(99, 446)	<.001	2.55	(−27, 45)	.887
Grade									
Well-differentiated (reference)									
Moderately differentiated	117.8	(−10, 305)	.076	−62.4	(−167, 97)	.389	85.09	(32, 158)	<.001
Urban/rural status									
Nonmetropolitan (reference)									
Metropolitan	135.1	(8, 320)	.035	103.3	(−38, 311)	.178	51.01	(7, 113)	.02
Stage									
Local/regional (reference)									
Distant	531.8	(315, 832)	<.001	242.4	(74, 483)	.002	303.2	(206, 432)	<.001

(continued)

Table 2. (continued)

	Overall incremental monthly costs compared to reference			Incremental inpatient monthly costs compared to reference			Incremental outpatient monthly costs compared to reference		
	Estimate ($)	CI	p value	Estimate ($)	CI	p value	Estimate ($)	CI	p value
Unknown	−44.4	(−146, 113)	.522	−81.5	(−215, 128)	.387	−11.2	(−47, 42)	.631
Chemotherapy									
No (reference)									
Yes	1272	(896, 1,773)	<.001	269.3	(96, 516)	<.001	994.4	(762, 1293)	<.001
Radiotherapy									
No (reference)									
Yes	820.3	(490, 1,286)	<.001	198.6	(−6, 502)	0.058	625.3	(441, 872)	<.001
Resection of primary tumors									
No (reference)									
Yes	563.8	(365, 832)	<.001	342	(161, 597)	<.001	−77.5	(−91, −55)	<.001
Resection of liver metastasis									
No (reference)									
Yes	973.1	(465, 1,747)	<.001	976.8	(471, 1733)	<.001	149	(30, 330)	.008
Region									
Midwest (reference)									
Northeast	89.89	(−49, 298)	.243	132.3	(−39, 387)	0.151	14.8	(−30, 80)	.571
South	−198	(−264, −87)	.002	−322	(−383, −212)	<.001	−30.7	(−62, 17)	.178
West	−22.9	(−129, 140)	.741	1.64	(−132, 204)	0.984	4.65	(−35, 63)	.847
Census tract % with at least high school diploma education in quartile									
1st quartile (reference)									
2nd quartile	−88.5	(−169, 37)	.145	−149	(−237, −9)	.039	−32.6	(−61, 10)	.118
3rd quartile	−49.6	(−147, 101)	.46	−99.7	(−209, 70)	.213	−41.2	(−70, 4)	.067
4th quartile	−116	(−208, 31)	.108	−107	(−226, 81)	.224	−66.2	(−93, −24)	.005
Census tract median income in quartile									
1st quartile (reference)									
2nd quartile	30.97	(−93, 218)	.677	−106	(−222, 76)	.216	59.32	(6, 135)	.024
3rd quartile	85.92	(−87, 352)	.386	−26.3	(−201, 249)	.819	64.79	(−2, 163)	0.06
4th quartile	250.5	(8, 622)	.041	153.1	(−99, 545)	.28	134.2	(41, 271)	.002
Census tract % below poverty level in quartile									
1st quartile (reference)									
2nd quartile	40.35	(−74, 211)	.547	15.16	(−115, 211)	.849	10.72	(−28, 68)	.642
3rd quartile	276.5	(63, 594)	.006	200.5	(−24, 539)	.088	54.02	(−8, 145)	.099
4th quartile	183.4	(−37, 524)	.119	80.6	(−149, 441)	.556	50.13	(−21, 156)	.196

Abbreviation: CI, confidence interval.

Table 3. Multivariate Regression Analysis for the cohort that died within the first year

| Parameter	Overall incremental monthly costs compared to reference			Incremental inpatient monthly costs compared to reference			Incremental outpatient monthly costs		
	Estimate	CI	p value	Estimate	CI	p value	Estimate	CI	p value
Carcinoid syndrome									
Yes	506.3	(−694, 3,317)	.535	−477	(−1608, 2829)	.669	260.2	(−28, 1009)	.1
No (reference)									
Age									
65–69 (reference)									
70–74	−1,021	(−2,054, 2,087)	.385	−2,132	(−3,139, 1,894)	.197	35.17	(−221, 872)	.875
75–79	−1,693	(−2,408, 819)	.131	−1,532	(−2,799, 2,948)	.356	−290	(−375, 188)	.149
≥80	−1,630	(−2,289, 672)	.119	−3,068	(−3,498, −359)	.035	−357	(−398, 9)	.053
Gender									
Female (reference)									
Male	−944	(−1,454, 598)	.163	−1,270	(−1,928, 1,032)	.189	64.32	(−109, 557)	.62
Race									
Non-Hispanic white (reference)									
Non-Hispanic black	959.5	(−798, 5,169)	.402	1,165	(−1,179, 7,365)	.471	−59.6	(−254, 623)	.771
Hispanic or others	3,157	(214, 9,779)	.028	2,459	(−770, 10,783)	.203	−283	(−385, 255)	.188
Comorbidity score									
0 (reference)									
1	3,046	(636, 8,100)	.003	3,797	(515, 11,326)	.011	100.9	(−140, 809)	.573
2	4,407	(1,217, 11,066)	<.001	5,205	(1,047, 14,695)	.003	−128	(−281, 456)	.509
≥3	4,185	(1,346, 9,925)	<.001	4,944	(1,213, 13,194)	<.001	281.2	(−46, 1,154)	.129
Site									
Larynx, bronchus, lung, trachea, and other (reference)									
Cecum and appendix	−38.2	(−2,225, 6,361)	.984	−1035	(−3,361, 7,140)	.684	−655	(−643, −134)	.029
Colon	−2,644	(−3,122, −294)	.036	−4072	(−4,343, −1,119)	.02	68.46	(−237, 1,077)	.792
Others	−3,711	(−3,470, −2,994)	<.001	−5,457	(−4772, −4838)	<.001	51.39	(−192, 818)	.801
Small intestine	1,435	(−405, 5,635)	.177	1,868	(−655, 8,176)	.218	−77.4	(−244, 511)	.675
Grade									
Well-differentiated (reference)									
Moderately differentiated	−1,220	(−1,941, 1,048)	.202	−2,078	(−2,813, 965)	.124	50.67	(−174, 744)	.785
Urban/rural status									
Nonmetropolitan (reference)									
Metropolitan	263.8	(−1,213, 4,006)	.816	837.7	(−1,429, 7,013)	.616	−93.7	(−266, 531)	.635
Stage									
Local/regional (reference)									
Distant	−286	(−1,308, 2,393)	.755	−1,799	(−2,528, 1,036)	.145	560.3	(96, 1,705)	.005
Unknown	−30.5	(−1,338, 3,359)	.977	188.4	(−1,714, 5,583)	.905	−50	(−245, 623)	.803

(continued)

Table 3. (continued)

Parameter	Overall incremental monthly costs compared to reference			Incremental inpatient monthly costs compared to reference			Incremental outpatient monthly costs		
	Estimate	CI	p value	Estimate	CI	p value	Estimate	CI	p value
Chemotherapy									
No (reference)									
Yes	−1,970	(−2,443, −45)	.047	−5,898	(−4,997, −5,701)	<.001	1811	(723, 4,198)	<.001
Radiotherapy									
No (reference)									
Yes	−3,092	(−3,288, −1,374)	.007	−6,570	(−5,581, −6,154)	<.001	802.7	(152, 2,450)	.003
Resection of primary tumors									
No (reference)									
Yes	6,194	(2,588, 13,165)	<.001	6,586	(2,235, 15,795)	<.001	−70.2	(−218, 440)	.664
Resection of liver metastasis									
No (reference)									
Yes	1,336	(−2,880, 15,434)	.698	1,148	(−3,930, 20,282)	.801	155.7	(−479, 3043)	.799
Region									
Midwest (reference)									
Northeast	−348	(−1,795, 3,667)	.792	−1,078	(−2,716, 4,373)	.558	44.14	(−240, 990)	.859
South	−1,814	(−2,447, 512)	.095	−3,306	(−3,692, −568)	.029	−316	(−387, 127)	.108
West	−1,810	(−2,485, 645)	.108	−2,144	(−3,135, 1,834)	.191	166.7	(−161, 1,159)	.48
Census tract % with at least high school diploma education in quartile									
1st quartile (reference)									
2nd quartile	45.97	(−1,287, 3,469)	.966	−215	(−1,893, 4,706)	.888	295.3	(−73, 1,319)	.177
3rd quartile	−1,241	(−2,182, 1,711)	.289	−2,232	(−3,185, 1,680)	.173	119.4	(−182, 1,051)	.605
4th quartile	−2,809	(−3,199, −641)	.023	−4,258	(−4,430, −1,515)	.014	−177	(−358, 583)	.478
Census tract median income in quartile									
1st quartile (reference)									
2nd quartile	1,861	(−493, 7,402)	.171	848.3	(−1,633, 7,780)	.649	109.4	(−199, 1,084)	.652
3rd quartile	4,592	(387, 14,500)	.022	4075	(−754, 17,120)	.141	256.4	(−211, 1,775)	.447
4th quartile	7,043	(1.184, 21,041)	.006	8173	(621, 28,296)	.023	74.23	(−342, 1,632)	.845
Census tract % below poverty level in quartile									
1st quartile (reference)									
2nd quartile	−315	(−1,655, 3,336)	.794	−580	(−2,316, 4,817)	.737	41.22	(−229, 930)	.861
3rd quartile	2,083	(−971, 9,870)	.273	2024	(−1,789, 13,064)	.448	−105	(−375, 977)	.736
4th quartile	2,385	(−1,125, 1,1641)	.28	1647	(−2,361, 14,016)	.588	−93.6	(−419, 1275)	.802

Abbreviation: CI, confidence interval.

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A

B

C
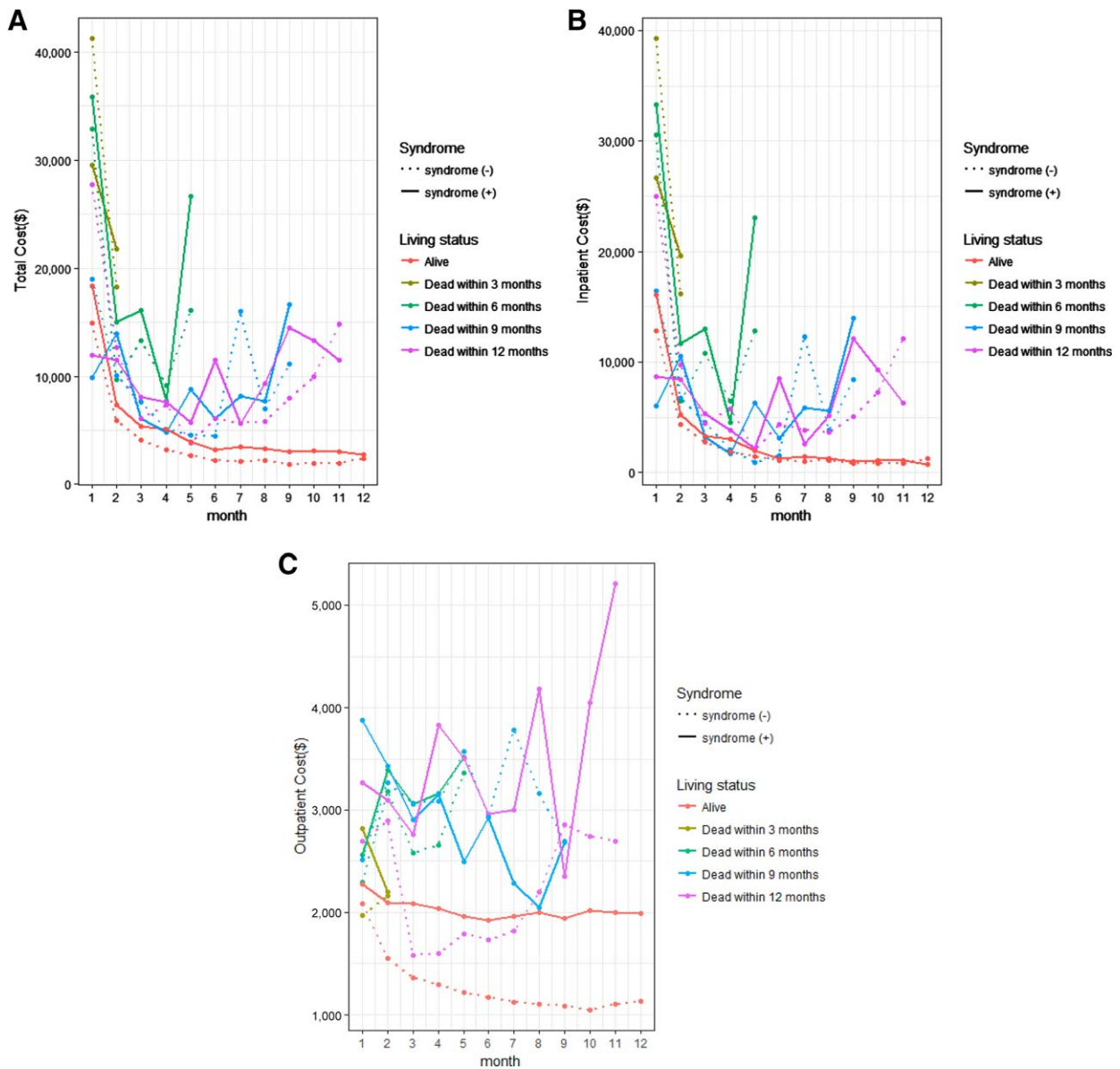
Figure 1. (A): Total costs by month after diagnosis. **(B)**: Inpatient costs by month after diagnosis. **(C)**: Outpatient costs by month after diagnosis. Abbreviations: syndrome, carcinoid syndrome.

approval because all patients in the database had been deidentified.

Results

Table 1 provides the descriptive statistics of the study sample by vital status and whether carcinoid syndrome was present. There were 5,633 patients who were alive throughout the first year and 1,116 patients who died within the first year of diagnosis. Among the patients that survived the whole first year after diagnosis, 1,189 (21%) had carcinoid syndrome; there were group differences in terms of the presence of carcinoid syndrome by gender; race; histologic stage; grade; primary tumor site; and treatment received, including chemotherapy, radiotherapy, and resection of liver metastasis. Among the group who died within the first year, 296 (26.5%) had carcinoid syndrome. In this group, we found differences in the proportion with carcinoid syndrome by gender, comorbidities, histologic stage, grade, primary tumor site, radiotherapy, and resection of primary tumors.

More importantly, Table 1 shows that there are significant differences in terms of costs for patients with and without carcinoid syndrome. Among the cohort who survived the whole first year after diagnosis, the patients with carcinoid syndrome had a median monthly total cost of $3,802, which is significantly higher ($p < .0001$) than $2,481 for patients without syndrome. Both outpatient and inpatient median monthly costs were also significantly higher ($p < .0001$) for patients with carcinoid syndrome compared with those without syndrome ($1,151 vs. $679 and $2,254 vs. $1,625, respectively). Similarly, among patients who died within the first year, the presence of carcinoid syndrome was associated with higher costs. Patients who died within the year had much higher monthly costs than patients who survived the first year as expected. We also found that among patients who survived the first year, those with the syndrome were significantly ($p < .001$) more likely to have ER admissions and hospitalization; among patients who died within the first year, the association remained significant

Table 4. Comparison of the non-somatostatin-analogue-related costs between patients with or without syndrome in the cohort alive throughout the first year

	With syndrome (n = 1,092)	Without syndrome (n = 3,975)	p value
Total monthly costs excluding somatostatin-analogue-related costs ($)			< .0001
Mean (SD)	4,073.78 (3,501.48)	3,121.87 (3,232.27)	
Median	3,318.23	2,437.81	
Outpatient monthly costs excluding somatostatin-analogue-related costs ($)			< .0001
Mean (SD)	1,252.69 (1,289.17)	993.32(1,127.85)	
Median	868.41	664.08	
Inpatient monthly costs excluding somatostatin-analogue -related costs ($)			< .0001
Mean (SD)	2,821.09 (3,051.76)	2,128.55 (2,759.75)	
Median	2,251.39	1,625.35	

(p = .007) for hospitalizations but was insignificant (p = .068) for ER admissions.

The results from the multivariable GLM analyses are presented in Table 2 and Table 3 for the cohort alive throughout the first year and the cohort who died within the first year, respectively. Among patients alive throughout the first year of diagnosis, carcinoid syndrome was associated with significantly higher total costs ($505), higher inpatient costs ($188), and higher outpatient costs ($294), with p values less than .005 even after controlling for clinical factors, treatment received, patient demographics, comorbidities, and neighborhood SES. The analyses also showed that the comorbidities had a large impact on the health care costs. Patients who had a comorbidity score above two were estimated to incur $594 more total monthly costs compared with patients who had zero comorbidity. Patients with distant stage NET had higher overall, inpatient, and outpatient costs than patients who had local or regional stage disease ($532, p < .001; $242, p = .002; and $303, p < .001, respectively).

Among the group who died within the first year of diagnosis, the association between carcinoid syndrome and costs were much less prominent. The associations for total, inpatient, and outpatient monthly costs were no longer significant at p values of 0.535, 0.669, and 0.1, respectively.

Figure 1A–1C depict the time trend pattern of monthly costs during the first year of diagnosis for total, inpatient, and outpatient costs. Figure 1A shows that all patients incurred high costs in the initial months; patients who survived the whole year had much lower costs after the initial time period, while patients who died within the first year incurred high costs towards the end of life and showed a classic U-shape with high costs during initial and terminal phases. Figure 1A also shows that patients with carcinoid syndrome had higher costs than patients without. Figure 1B showed a similar time trend for inpatient costs. Patient who survived the whole year had a downward trend in inpatient costs, while patients who died had a U-shaped curve. The difference between patients with and without syndrome was not as obvious as in Figure 1A. Figure 1C shows the pattern for outpatient costs. It is interesting that among patients alive throughout the first year, those without the syndrome had a substantial drop in outpatient costs, while patients with the syndrome maintained a stable outpatient cost during the year. Figure 1C also showed that the outpatient costs for patients who died within the year did not show the U-shape observed in total and inpatient costs.

DISCUSSION

This study is the first one in the literature that examines the health care costs associated with carcinoid syndrome among NET patients. We compared the overall, inpatient, and outpatient costs between patients with and without the syndrome from the payer's perspective. We separately analyzed patients who survived the first year of diagnosis and patients who died within the first year. Among patients alive throughout the first year, the unadjusted analyses showed that total median monthly costs were above $1,000 higher ($3,801 vs. $2,481) for patients with the syndrome compared with patients without, with approximately half of the difference each coming from inpatient and outpatient costs. We found that carcinoid syndrome was significantly associated with higher health care costs including overall, inpatient and outpatient costs even after controlling for clinical factors, treatment received, demographics, and neighborhood SES among patients throughout the first year. We found that patients with a comorbidity score above two incurred much higher costs compared to patients who had no comorbidities. This finding is consistent with the literature on the impact of comorbidities on health care costs among cancer patients. For example, one study on newly diagnosed cancer patients found that patients with four or more comorbid conditions were much more likely (OR = 2.5, 95% CI: 2.26 to 2.76) to be in the top 10% in terms of health spending [17]. Another study estimated that the increase in cancer treatment cost associated with the chronic conditions during the first 6 months after cancer diagnosis ranged from $4,385 for cardiac disease to $11,009 for mental health disorders [18]. Our estimates of increase in health care costs per month ranging from $296 to $1,359 depending on the number of comorbidities is in line with the above estimates and confirms the large impact of comorbidities on health care costs in the NET population.

As patients with the syndrome were much more likely to receive somatostatin analog, which could be a major source of higher cost, we further examined the overall, inpatient, and outpatient costs, excluding somatostatin analog related claims. We identified claims related to somatostatin analog usage based on Healthcare Common Procedure Coding System codes (J-2353, J-2352, J-1930) and National Drug Code codes

(00078034061, 00078034084, 00078034161, 00078034184, 00078034261, 00078034284, 15054006001, 15054009001, 15054012001, 15054012002). The detailed results are presented in Table 4. We found that the median overall monthly cost of patients with the syndrome was reduced by about $600 a month after excluding somatostatin analog-related costs with most of the difference originating from outpatient costs, while the median costs for patients without the syndrome did not change much after the exclusion. After excluding somatostatin analog-related costs, the difference in outpatient costs was much smaller at around $200. However, patients with the syndrome still had higher inpatient costs than patients without the syndrome. It suggests that patients with the syndrome have a higher disease burden even after controlling for the use of symptom control drugs, or that initial therapy involves more frequent use of surgery and/or selective internal radiotherapy in the inpatient setting to reduce symptom burden in patients with carcinoid syndrome. This is in line with our finding in Table 1 that patients with the syndrome were much more likely to have ER admission and hospitalizations. This could be related to delayed initiation of somatostatin analogue therapy after diagnosis. Secondly, even in patients initiated on somatostatin analogue therapy, they could be on subtherapeutic doses. In fact, we have previously shown that the majority of elderly patients with carcinoid syndrome do not have somatostatin analogue therapy initiated within the first 6 months after diagnosis [19], and even in those who received somatostatin analogue therapy, 36% received dosages lower than the recommended 20 mg per 28 days [20]. Further, data from clinical studies of octreotide showed that patients who received appropriate therapy may have improved but still residual diarrhea [8]. Finally, these inpatient admissions and ER visits could be related to other complications of carcinoid syndrome, such as abdominal cramping or carcinoid heart disease.

Patients who died within the first year incurred much higher costs, with total monthly costs above $15,000 regardless of carcinoid syndrome presence. Among this group, after adjusting for clinical factors, treatment received, demographics, and neighborhood SES, the significant association between carcinoid syndrome and costs vanished. This is probably due to the overwhelmingly higher cost of terminal care, which is often accompanied by more frequent hospital admissions than earlier phases of disease.

Additionally, we showed the time pattern of health care costs incurred during the first year. All NET patients incurred very high costs during the initial months, when a substantial amount of diagnostic testing and possible interventions (such as surgeries) occur. The total cost in the first month was above $10,000 for almost all patients and was above $30,000 for some groups. Patients who survived had a clear downward trend in total costs, stabilizing around $3,000 in later months, while patients who died had the typical U-shaped curve showing high terminal care costs. The figures also showed that the high terminal care was mostly originated from high inpatient costs, while outpatient costs were much lower. One interesting observation is that among patients who survived the whole year, outpatient costs dropped significantly towards the later months for those who did not have carcinoid syndrome, while outpatient costs remained high during the whole year for those who had carcinoid syndrome. This is probably because

some patients who did not have syndrome might have been on active surveillance without much need for office visits, while patients with the syndrome visited the physician's office regularly for somatostatin analogues treatment to control the symptoms. Additionally, since carcinoid syndrome is generally associated with more advanced stages of disease, it is possible that patients with carcinoid syndrome were seen more often due to complications of more advanced disease.

Our study is based on SEER-Medicare data and, therefore, has the limitations common among observational studies. First, the presence of carcinoid syndrome was derived from Medicare claims. It is possible that there might be miscoding and inaccuracies in the claims. Second, in this study we focused on the health care costs of NET patients during the first year after diagnosis, for which we have sufficient complete data. In examining the health care cost time pattern for patients who survived the full year and patients who died within the year, we found that patients who survived the first year had relatively stable costs during the second half of the year, while patients who died showed high terminal care costs. Therefore, we expect that patients who survived for more than 1 year will continue to have reasonably stable health care costs at a level close to the end of the first year until they reach their terminal phase when the costs rise up again. Last, we focused on elderly patients because the data source used was SEER-Medicare and the Medicare program mainly covers patients above 65 years old. This may limit the generalizability of this study to younger groups who are more likely to have private insurance, possibly of greatest relevance in thymic and appendiceal NETs, which have younger median ages of diagnosis. Nevertheless, as Medicare is the single largest payer for health care in the U.S. and Medicare reimbursement rate is widely accepted as a benchmark in the industry, studying the health care costs from the perspective of Medicare is common and widely accepted in the literature [21].

Of particular note, the temporal pattern of resource utilization is different for patients with carcinoid syndrome as compared with that of patients with nonfunctional tumors. Therefore, it is less likely that patients with carcinoid syndrome merely represent a more advanced stage of the same disease, and, rather, suggests that carcinoid syndrome is an independent predictor of health care costs. An economic argument for improved carcinoid syndrome control is therefore feasible, depending upon the cost of any intervention to further reduce symptom burden and the resultant health care costs.

CONCLUSION

This study demonstrated and quantified for the first time in the literature the additional costs associated with carcinoid syndrome in elderly NET patients during the first year of diagnosis. Such information may help stakeholders in the health care industry to efficiently allocate resources for NET patients.

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Data analysis and interpretation: Chan Shen, Yiyi Chu, Daniel M. Halperin, Arvind Dasari, Shouhao Zhou, Ying Xu, James C. Yao, Ya-Chen Tina Shih

Manuscript writing: Chan Shen, Yiyi Chu, Daniel M. Halperin, Arvind Dasari, Shouhao Zhou, Ying Xu, James C. Yao, Ya-Chen Tina Shih

Final approval of manuscript: Chan Shen, Yiyi Chu, Daniel M. Halperin, Arvind Dasari, Shouhao Zhou, Ying Xu, James C. Yao, Ya-Chen Tina Shih

Disclosures

Daniel Halperin: Novartis (C/A, RF), Ipsen, Dicerna, Genentech/Roche (RF), Oxigene (C/A). The other authors indicated no financial relationships.

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References

1. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–3072.

2. Shen C, Dasari A, Zhao B et al. Incidence and prevalence of neuroendocrine tumors in the United States 1973–2012. Paper presented at: NANETS Symposium 2016; Jackson, Wyoming.

3. Dasari A, Shen C, Halperin D et al. Survival trends of neuroendocrine tumors and associated prognostic factors. Paper presented at: NANETS Symposium 2016; Jackson, Wyoming.

4. Beaumont JL, Cella D, Phan AT et al. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas 2012;41:461–466.

5. Davis Z, Moertel CG, McIlrath DC. The malignant carcinoid syndrome. Surg Gynecol Obstet 1973;137:637–644.

6. Kvols LK, Martin JK, Marsh HM et al. Rapid reversal of carcinoid crisis with a somatostatin analogue. N Engl J Med 1985;313:1229–1230.

7. Kvols LK, Moertel CG, O'Connell MJ et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986;315:663–666.

8. Rubin J, Ajani J, Schirmer W et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol 1999;17:600–666.

9. Overview of the SEER Program. Available at http://seer.cancer.gov/about/overview.html. Accessed May 19, 2017.

10. Warren JL, Klabunde CN, Schrag D et al. Overview of the SEER-Medicare data: Content, research applications, and generalizability to the United States elderly population. Med Care 2002;40(suppl 8):IV3–IV18.

11. Databases, Tables & Calculators by Subject. Available at http://www.bls.gov/data/. Accessed May 19, 2017.

12. Shen C, Shih YC, Xu Y et al. Octreotide long-acting repeatable among elderly patients with neuroendocrine tumors: A survival analysis of SEER-Medicare data. Cancer Epidemiol Biomarkers Prev 2015;24:1656–1665.

13. Halperin DM, Shen C, Dasari A et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: A population-based study. Lancet Oncol 2017;18:525–534.

14. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.

15. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.

16. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: Differing perspectives. J Clin Epidemiol 1993;46:1075–1079.

17. Wodchis W, Arthurs E, Khan A et al. Cost trajectories for cancer patients. Curr Oncol 2016;23(suppl 1):S64–S75.

18. Subramanian S, Tangka FK, Sabatino SA et al. Impact of chronic conditions on the cost of cancer care for Medicaid beneficiaries. Medicare Medicaid Res Rev 2013;2:4.

19. Shen C, Shih YC, Xu Y et al. Octreotide long-acting repeatable use among elderly patients with carcinoid syndrome and survival outcomes: A population-based analysis. Cancer 2014;120:2039–2049.

20. Shen C, Xu Y, Dasari A et al. Octreotide LAR dosage and survival among elderly patients with distant-stage neuroendocrine tumors. *The Oncologist* 2016;21:308–313.

21. Riley GF. Administrative and claims records as sources of health care cost data. Med Care 2009;47:S51–S55.

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