Predictive Factors of Carcinoid Syndrome (CS) among Patients with Gastrointestinal Neuroendocrine Tumors (GI NETs) Beilei Cai, PhD¹, Michael S. Broder, MD, MSHS², Eunice Chang, PhD², Tingjian Yan, PhD², David C. Metz, MD³ ¹ Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936; ² Partnership for Health Analytic Research, LLC, Beverly Hills, CA 90212; ³ University of Pennsylvania, Philadelphia, PA 19104

BACKGROUND

- Carcinoid syndrome (CS) affects approximately 34% of small bowel NETs patients¹ and is associated with significant symptoms and decreased quality of life.²
- Patients may experience long delays in diagnosis with a median time from onset of symptoms to diagnosis from 2 to 20 years.³
- There is limited information on the existence of predictors associated with the development of CS.
- This study attempts to detect factors predictive of CS prior to diagnosis among patients with an established diagnosis of gastrointestinal neuroendocrine tumor (GI NET).

METHODS

Study Design and Data Source

• Matched case-control study using data from two large U.S. healthcare claims databases – IMS PharMetrics Plus (development database) and Truven Health Analytics MarketScan (validation database) between 1/1/2009 and 12/31/2014.

Study Population Identification

- Adult patients \geq 18 years old newly-diagnosed with GI NETs during the study identification period (1/1/2010 – 12/31/2014) with at least 1 inpatient or 2 outpatient claims with ICD-9-CM codes for GI NET (209.0, 209.1, 209.2, 209.4, 209.5, and 209.6).
 - Excluded patients with GI NETs in 1-year prior to first diagnosis date for GI NETs and those with pancreatic NETs and Merkel cell carcinoma (MCC)
- Patients with GI NETs without CS (controls) matched to those with CS (cases) based on diagnosis date (month and year) of first GI NET diagnosis at a 3-to-1 ratio
 - CS identified using 2 claims with ICD-9-CM code 259.2 and either
 - urine 24-hour 5-HIAA test (CPT code: 83497) or serum serotonin test (CPT code: 84260) ordered in period 3 months before or 3 months after CS diagnosis
- Index date for cases was first CS diagnosis date. Index date for controls was assigned to have the same distance from date of first NET diagnosis as matched case patients.
- All patients required to have at least 1-year continuous enrollment prior to index date (study baseline).

Statistical Analysis

• Logistic regression used to identify risk factors

Figure 1. Patient Identification Flo



RESULTS

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owchart	Table 1. Patient Demographics								
atient claim or 2 outpatient claims with	Development Database					Validation Database			
riod (1/1/2010-12/31/2014)		CS Cohort	Non-CS Cohort	All	P Value	CS Cohort	Non-CS Cohort	All	P Value
,287 patients without 1-year continuous nrollment prior to the first selected NET	Ν	251	753	1,004		181	543	724	
diagnosis	Age, year, mean (SD)	52.8 (10.88)	54.4 (13.28)	54.0 (12.74)	0.058	51.8 (9.33)	51.7 (10.03)	51.7 (9.85)	0.913
201 patients with NET diagnosis of any type in 1-year prior to the first NET diagnosis (not newly diagnosed)	Age, year, n (%)				0.034				0.637
					0.054				0.037
8 patients with either pancreatic NETs or	18-44	52	143	195		33	100	133	
CC, or without GI, lung, other/unknown,		(20.7)	(19.0)	(19.4)		(18.2)	(18.4)	(18.4)	
or secondary NETs during study period	45-54	80	219	299		64	203	267	
		(31.9)	(29.1)	(29.8)		(35.4)	(37.4)	(36.9)	
3.244 not meeting diagnostic criteria (2	55-64	94	257	351		83	231	314	
claims with CS and 5-HIAA or serum		(37.5)	(34.1)	(35.0)		(45.9)	(42.5)	(43.4)	
erotonin +/- 90s days around first CS dx	65+	25	134	159		1	9	10	
date (index date)		(10.0)	(17.8)	(15.8)		(0.6)	(1.7)	(1.4)	
	Female, n	133	407	540	0.770	109	297	406	0.195
4 patients <18 years old	(%)	(52.0)	([] 4])	(52.0)		(co a)			
	Region n	(53.0)	(54.1)	(53.8)		(60.2)	(54.7)	(56.1)	
	(%)				0.206				0 667
281 patients without CS diagnosis	Midwest	67	219	286	0.300	37	118	155	0.007
nd without 1-year continuous enrollment		(26.7)	(29.1)	(28.5)		(20.4)	(21.7)	(21.4)	
prior to index date	Northeast	57	200	257		41	100	141	
		(22.7)	(26.6)	(25.6)		(22.7)	(18.4)	(19.5)	
5 patients who could not be matched	South	106	269	375		80	254	334	
		(42.2)	(35.7)	(37.4)		(44.2)	(46.8)	(46.1)	
	West	21	65	86		23	71	94	
		(8.4)	(8.6)	(8.6)		(12.7)	(13.1)	(13.0)	

• In the development database, 1,004 patients with GI NETs were identified, among whom 251 (25%) had CS (cases) and 753 (75%) were (controls) (Figure 1). In the validation database, 724 patients with GI NETs were identified, including 181 (25%) cases and 543 (75%) controls (Table 1).

• There were no significant differences in age, sex, and U.S. geographical region between cases and controls.

• A total of 33 of the most common, relevant conditions in both cases and controls of the development database were identified, with abdominal pain (66.1% of CS cohort; 51.5% of non-CS cohort), hypertension (50.6%; 52.2%), and dyslipidemia (49.4%; 46.1%) the most prevalent diagnoses.

• In the final, validated model, three factors prior to CS diagnosis were associated with higher CS risk, including liver disorder [OR (95% confidence interval (CI)) 3.38 (2.07-5.51)], enlarged lymph nodes [2.13 (1.10-4.11)], and abdominal mass [3.79 (1.87-7.69)] (Table 2).



CONCLUSIONS

- This study in two large databases covering nearly 200 million insured Americans suggests that patients diagnosed with CS are 2-4 times as likely to have a preexisting liver disorder, enlarged lymph nodes, or abdominal mass compared to those without CS, within 1-year prior to CS diagnosis.
- These findings may aid physicians in diagnosing patients with CS earlier, thus aiding quality of life and survival.
- Future database studies to further validate the findings are warranted.

Table 2. Results of Final Model

	Development D	atabase	Validation Database			
Independent Variable	OR (95% CI)	P Value	OR (95% CI)	P Value		
Age group						
18-44 vs 65+	2.30 (1.26 - 4.23)	0.007	4.88 (0.56 - 42.11)	0.150		
45-54 vs 65+	1.94 (1.14 - 3.31)	0.015	3.63 (0.43 - 30.41)	0.235		
55-64 vs 65+	2.01 (1.20 - 3.38)	0.008	3.85 (0.46 - 31.93)	0.212		
Number of chronic conditions	0.94 (0.87 - 1.01)	0.093	1.13 (1.02 - 1.24)	0.014		
Abdominal pain	1.50 (1.08 - 2.09)	0.016	1.22 (0.83 - 1.77)	0.309		
Dyslipidemia	1.52 (1.08 - 2.15)	0.016	0.83 (0.55 - 1.25)	0.373		
Diverticulosis of colon	1.55 (1.08 - 2.24)	0.019	1.16 (0.72 - 1.86)	0.537		
Liver disorder	2.12 (1.40 - 3.20)	<0.001	3.38 (2.07 - 5.51)	<0.001		
Enlarged lymph nodes	2.33 (1.38 - 3.92)	0.001	2.13 (1.10 - 4.11)	0.025		
Type 2 diabetes	0.59 (0.38 - 0.92)	0.021	0.89 (0.54 - 1.48)	0.653		
Abdominal mass	1.89 (1.06 - 3.37)	0.031	3.79 (1.87 - 7.69)	<0.001		
Dyspepsia and other functional stomach disorders	2.95 (1.60 - 5.43)	<0.001	0.54 (0.23 - 1.26)	0.154		

LIMITATIONS

- GI NETs and CS diagnoses were identified from claims coded for reimbursement, not research, and misclassification was possible.
- We could not identify specific anatomic location of GI NETs, leading to possible confounding.
- Our results are reflective of a commercially-insured population, but may not be generalizable to patient populations with other insurance types.
- Study patients were identified using ICD-9-CM codes; pathologic diagnosis could not be confirmed in this administrative database.

References

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