Predictive Factors of Carcinoid Syndrome (CS) among Patients with Gastrointestinal Neuroendocrine Tumors (GI NETs)

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BACKGROUND

- Carcinoid syndrome (CS) affects approximately 34% of small bowel NETs patients[1] 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 ≥ 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 Flowchart

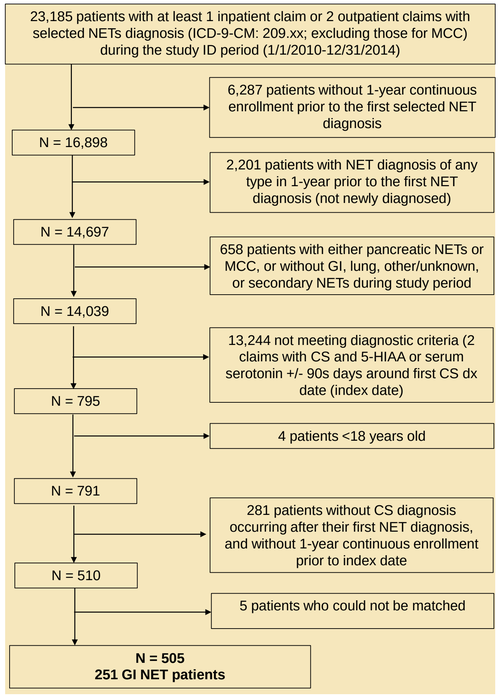

Table 1. Patient Demographics

	Development Database				Validation Database			
	CS Cohort	Non-CS Cohort	All	P Value	CS Cohort	Non-CS Cohort	All	P Value
N	251	753	1,004		181	543	724	
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
Age, year, n (%)				0.034				0.637
18-44	52 (20.7)	143 (19.0)	195 (19.4)		33 (18.2)	100 (18.4)	133 (18.4)	
45-54	80 (31.9)	219 (29.1)	299 (29.8)		64 (35.4)	203 (37.4)	267 (36.9)	
55-64	94 (37.5)	257 (34.1)	351 (35.0)		83 (45.9)	231 (42.5)	314 (43.4)	
65+	25 (10.0)	134 (17.8)	159 (15.8)		1 (0.6)	9 (1.7)	10 (1.4)	
Female, n (%)	133 (53.0)	407 (54.1)	540 (53.8)	0.770	109 (60.2)	297 (54.7)	406 (56.1)	0.195
Region, n (%)				0.306				0.667
Midwest	67 (26.7)	219 (29.1)	286 (28.5)		37 (20.4)	118 (21.7)	155 (21.4)	
Northeast	57 (22.7)	200 (26.6)	257 (25.6)		41 (22.7)	100 (18.4)	141 (19.5)	
South	106 (42.2)	269 (35.7)	375 (37.4)		80 (44.2)	254 (46.8)	334 (46.1)	
West	21 (8.4)	65 (8.6)	86 (8.6)		23 (12.7)	71 (13.1)	94 (13.0)	

RESULTS

- 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 Database		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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