SAT-0649

IDENTIFICATION OF POTENTIAL MARKERS FOR CUSHING'S DISEASE AS AN AID TO DIAGNOSIS

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BACKGROUND

- Cushing's disease (CD) is a rare endocrine disorder resulting from excess adrenocorticotropic hormone production from a pituitary tumor.[1] Because of the wide variety of nonspecific symptoms associated with CD, clinical suspicion may be difficult to elicit and many years typically elapse between symptom onset and diagnosis.[2]
- Using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, it may be possible to uncover previously unknown or unusual combinations of otherwise common symptoms, or "signals" associated with CD.

OBJECTIVE

- To identify and evaluate dyads and triads of clinical symptoms or conditions associated with CD, using commercial healthcare claims data.

METHODS

Study Design and Data Source

This was a retrospective matched case-control study using the Truven Health Analytics MarketScan® Database.

Study Population and Study Timeframe

Timeframe: Data spanned 1/1/2008 to 12/31/2012.

Inclusion Criteria for CD Patients:

- ≥1 medical claim with a diagnosis of Cushing's syndrome (CS; ICD-9-CM: 255.0) and ≥1 medical claim for pituitary neoplasm, disease, or surgery as previously described by Burton et al.[3]; AND
- continuous enrollment in the measurement year.

Inclusion Criteria for Matched Non-CD Patients: We included patients from a 5% random sample who

- had no medical claim with CS as one of the listed diagnoses in the identification (ID) period; AND
- were continuously enrolled in at least one calendar year in the ID period.

For non-CD patients who were continuously enrolled in more than one calendar year, we randomly picked one calendar year as their measurement year. Two non-CD patients with the same age, gender, and region in the same measurement year were randomly selected and matched to each CD patient.

Study Measures

- Patient demographics: age, gender, region
- 46 unique symptoms and comorbid conditions, identified with expert input

Analytical Datasets

- We randomly split CD patients to either the development or validation dataset. The matched controls were assigned to either the development or validation dataset accordingly.
- **Development dataset**: For all cases and controls in the development dataset, 45 patient characteristics and Cushing's disease-related clinical characteristics were evaluated, as well as 169 dyads and 424 triads of those characteristics.
- **Validation dataset**: With expert endocrinologist input, we isolated 10 key patient characteristics and 6 uncommon dyads of clinical significance and applied these to the validation dataset.
  - Key characteristics: hirsutism, localized adiposity, facial plethora, polycystic ovary syndrome, deep venous thrombosis, hypokalemia, abnormal weight gain, muscle weakness, osteoporosis, female balding

Statistical Analyses

- Frequencies and prevalence rates, as well as CD and non-CD relative risk (RR), were calculated.
- SAS® version 9.4 (SAS Institute, Cary, NC)

RESULTS

- 3,750 patients with CD were matched with 7,500 patients without CD; entire cohort of 11,250 patients was divided equally between development and validation datasets. **Tables 1 and 2** provide final results following expert review.

Development Dataset

- Mean age 41.1 years; 76.8% female
- **Hirsutism** was associated with the highest RR among CD patients (27.8); acne had the lowest RR (1.9).
  - Adrenal mass, striae, and abnormal genital virilization were observed only in CD patients.
- **Hypertension/hirsutism** was associated with the highest RR (70.0); hypertension/hyperlipidemia had the lowest RR (2.7).
  - Eighteen dyads were observed only in CD patients.
- 57 dyads were associated with higher-than-expected RR
  - Expected RR was calculated by assuming that risks of component conditions were independent.
  - In 7 dyads, observed RR was more than double the expected RR.
- **Hypertension/abnormal weight gain/headache** was associated with the highest RR (114.0).
  - Forty-eight triads were observed only in CD patients.

Validation Dataset

- Mean age 41.0 years; 76.4% female
- Abnormal weight gain had the highest prevalence in CD patients (11.7%); localized adiposity had the lowest prevalence (0.4%).
  - Localized adiposity was observed only in CD patients.
- **Hirsutism** was associated with RR of 61.0, highest in the validation list and over twice the RR as observed in the development dataset.

TABLES

Table 1. Relative Risk of Potential CD-Related Conditions Selected via Expert Opinion

Condition	Development Dataset	Validation Dataset		
	RR	Frequency (%) in CD Patients	Frequency (%) in Non-CD Patients	RR
Localized adiposity	18.0	8 (0.4%)	0 (0%)	∞
Hirsutism	27.8	122 (6.5%)	4 (0.1%)	61.0
Facial plethora	15.0	21 (1.1%)	2 (0.05%)	21.0
Polycystic ovary syndrome	11.7	148 (7.9%)	20 (0.5%)	14.8
Abnormal weight gain	9.4	219 (11.7%)	39 (1.0%)	11.2
Hypokalemia	10.2	130 (6.9%)	28 (0.7%)	9.3
Deep venous thrombosis	10.8	49 (2.6%)	13 (0.3%)	7.5
Muscle weakness	8.0	73 (3.9%)	20 (0.5%)	7.3
Female balding	5.1	56 (3.0%)	16 (0.4%)	7.0
Osteoporosis	6.2	170 (9.1%)	64 (1.7%)	5.3

Legend: CD = Cushing's disease; RR = relative risk.

RR is the relative risk of a condition in patients with Cushing's disease vs. non-Cushing's disease.

- Osteoporosis was associated with RR of 5.3, lowest in the list and slightly less than RR of 6.2 observed in the development dataset.
- **Hirsutism/fatigue** was associated with the highest RR (128.0), over 3½ times the RR observed in the development dataset.
  - Three dyads had an observed RR>100. All but one dyad had an RR>5.
  - Four dyads were observed only in CD patients
- Psychiatric disorders/serious infections was associated with the lowest RR (4.1), and the only dyad in the list with RR<5.

Table 2. Relative Risk of Dyads Selected via Expert Opinion [a]

Condition 1	Condition 2	Development Dataset	Validation Dataset		
		RR	Frequency (%) in CD Patients	Frequency (%) in Non-CD Patients	RR
Hypertension	Hirsutism	70.0	49 (2.6%)	0 (0%)	∞
Type 2 diabetes	Hirsutism	62.0	30 (1.6%)	0 (0%)	∞
Obesity	Osteoporosis	10.0	26 (1.4%)	1 (0.03%)	52.0
Weakness/fatigue	Female balding	15.3	30 (1.6%)	3 (0.08%)	20.0
Osteoporosis	Serious infections	15.1	66 (3.5%)	16 (0.4%)	8.3
Hypertension	Serious infections	4.6	269 (14.3%)	106 (2.8%)	5.1

Legend: CD = Cushing's disease; RR = relative risk (Cushing's disease vs. non-Cushing's disease).

[a] Only the 6 dyads to be validated further using binary classification tests are shown above. These 6 dyads were selected by a clinical content expert.

LIMITATIONS

- The databases included only commercially insured patients; the results may not necessarily be applicable to other populations, such as the uninsured.
- There may not be clinical consensus on what constitutes key patient characteristics in the CD population.
- MarketScan is a healthcare claims database intended for billing purposes, and not specifically for research. Coding of symptoms and conditions by healthcare providers may be inconsistent.

CONCLUSIONS

- Analysis of US healthcare claims database demonstrated that RR of having any one of 10 key conditions selected by expert opinion was at least 5 times greater in CD compared to non-CD. Nearly all dyads selected by expert endocrinologist opinion had RR at least 5 times or greater, however, construction of dyads resulted in further increases in RR beyond single condition analyses (osteoporosis alone had RR of 5.3, which increased to 8.3 with serious infections, and 52.0 with obesity).
- If clinicians consider the diagnosis of CD when the highest-risk conditions are seen, identification of this rare disease may improve. These results may be useful in developing clinical decision aids to identify patients at highest risk of CD.
- Future research will use binary classification tests to validate the ability of the 10 conditions and 6 dyads reviewed in this study to predict the diagnosis of CD in a heterogeneous cohort of patients.

REFERENCES

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