BACKGROUND

- Cushing's disease (CD) is a rare endocrine disorder resulting from excess adrenocorticotropic hormone production from a pituitary tumor. 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.
- Using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic 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 healthcare claims data.

METHODS

Study Design and Data Source

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

Study Population and Study Timeframe

- Time period: January 1, 2005 to December 31, 2011.
- Inclusion Criteria for CD Patients:
  - 21 medical claim with a diagnosis of Cushing's syndrome (ICD-9-CM: 258.0) and 2 medical claim for pharyngeal necrosis, disease, or surgery as previously described by Burton et al. 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 diagnosis codes in the identification (CD) period, AND
  - Were continuously enrolled in all at least one calendar year in the ID period.

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.
- Hirulutin was associated with the highest RR among CD patients (27.8); acne was associated with RR of 61.0, highest in CD patients.(CS; ICD-9-CM: 338.8; C8; ICD-9-CM: 314.0)
- Abnormal weight gain had the highest prevalence (15.7%)
- Hypertension/hirsutism had the lowest prevalence (0.5%) in CD patients.
- The only dyad in the list with RR<5.
- 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.

Analysed Results

- 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 644 triads of these characteristics.

METHODS (CONT.)

- 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, polyostotic bone disease, deep vein thrombosis, hypothyroidism, 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 (Cont.)

- 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.

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 several CD-related symptoms was greater in CD compared to non-CD. Nearly all dyads selected by expert endocrinologist opinion had RR at least 5 times greater, or higher. 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 venous infections, and 52.0 with obesity).
- It clinicians consider the diagnosis of CD when the highest-risk conditions are seen, identification of the 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 uncommon dyads reviewed in this study to predict the diagnosis of CD in a heterogeneous cohort of patients.