Identification of Potential Markers for Acromegaly as an Aid to Diagnosis

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BACKGROUND

- New data mining techniques for large databases have been developed and may be useful in medical care.
- These techniques may make it possible to uncover correlations to assist clinicians in diagnosing rare diseases.
- Due to slow tumor growth and non-specific symptoms, delay in diagnosis of acromegaly is common.[1-2]
- Therefore, we used acromegaly as an example and tested our ability to identify potential markers of disease.

OBJECTIVE

- To identify and evaluate dyads (pairs) of clinical conditions associated with acromegaly and to determine if such dyads could be used as disease markers.

METHODS

- Retrospective matched case-control design using MarketScan and PharMetrics databases from 1/1/2008 to 12/31/2013.

Inclusion Criteria

Acromegaly Patients

- ≥2 claims with ICD-9-CM code for acromegaly (253.0) or ≥1 such claim plus 1 for pituitary tumor or pituitary surgery.
- Continuous enrollment in the measurement year (i.e., the calendar year of the first acromegaly associated claim).

Matched Non-Acromegaly Controls

- Selected from 5% random sample with no claim for acromegaly diagnosis.
- Each acromegaly patient matched with 2 controls by age, gender, region, and measurement year.

Primary Outcome

- Relative risk of dyad combinations of 36 clinical conditions identified with expert endocrinologist input.

Analysis

- Cases and controls split randomly into development and validation datasets; risk conditions determined in the measurement year.
- Development dataset: investigated 630 dyad combinations by calculating prevalence rates and relative risk (RR) (compared to controls). Results reported for dyad combinations that met 1 of 2 criteria:
    1) case rate ≥5%, or a case rate ≥1% with RR ≥5; or
    2) observed RR > expected RR (assuming each clinical condition is independent).
- Validation dataset: 10 most prevalent dyad combinations meeting each criterion (total=20) selected for replication to confirm results.
- All analyses used SAS® version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Cohort

- 3731 cases and 7462 matched controls; overall mean age was 41.8 (SD 16.1), 51.8% of females, and all U.S. regions represented.
- Validation and development datasets had no statistically significant differences.

Individual Condition

- Hypertension (HTN) was most common among acromegaly patients (34.9%) and goiter least (0.1%; result not shown).
- Among conditions with rate ≥5% in acromegaly patients, sleep apnea was associated with the highest RR (3.9) and hypertension had the lowest RR of 1.7 compared to non-acromegaly controls (**Table 1**).

Table 1: Patient characteristics and relative risks of selected individual conditions

Patient Characteristics	Acromegaly Patients N=3731	Non-Acromegaly Controls N=7462	RR[a]
Age year Mean (SD)	41.8 (16.1)	41.8 (16.1)	
<=40	1408 (37.7)	2816 (37.7)	
41-50	943 (25.3)	1886 (25.3)	
51-64	1380 (37.0)	2760 (37.0)	
Female, n(%)	1934 (51.8)	3868 (51.8)	
Clinical Conditions, n(%)			
Sleep apnea	526 (14.1)	268 (3.6)	3.9
Valvular insufficiency	206 (5.5)	125 (1.7)	3.3
Arrhythmias	303 (8.12)	213 (2.9)	2.8
Metabolic disorder	974 (26.1)	705 (9.4)	2.8
Fatigue	721 (19.3)	572 (7.7)	2.5
Arthritis	491 (13.2)	391 (5.2)	2.5
Colon polyps	195 (5.2)	158 (2.1)	2.5
Menstrual abnormalities	315 (8.4)	275 (3.7)	2.3
Arthralgia	822 (22.0)	884 (11.8)	1.9
Hypertension	1302 (34.9)	1517 (20.3)	1.7

[a] Relative risk of individual conditions for acromegaly vs. non-acromegaly patients.
[b] Conditions with prevalence ≥5% in acromegaly were selected.

Selected Dyads of Conditions

- RRs varied from 13.5 for valvular insufficiency + colon polyps to 2.8 for arthralgia + hypertension (**Table 2**).

Table 2: Combined risk of selected conditions sorted by RR

Condition 1	Condition 2	RR[a] (95% CI)	Expected RR[b]
Valvular insufficiency	Colon polyps	13.5 (4.7 - 38.6)	8.1
Menstrual abnormalities	Sleep apnea	12.5 (4.4 - 35.9)	9.0
Metabolic disorder	Hyperhidrosis	12.0 (4.2 - 34.6)	11.9
Colonic diverticula	Sleep apnea	11.1 (5.0 - 24.9)	9.3
Arthropathy	Sleep apnea	10.0 (4.2 - 24.0)	9.1
Valvular insufficiency	Colonic diverticula	9.0 (3.7 - 21.8)	7.8
Metabolic disorder	Menstrual abnormalities	7.8 (4.7 - 12.9)	6.3
Arthralgia	Valvular insufficiency	6.6 (4.2 - 10.2)	6.1
Arthritis	Menstrual abnormalities	6.0 (2.6 - 14.1)	5.8
Metabolic disorder	Fatigue	5.8 (4.6 - 7.5)	7.0
Metabolic disorder	Sleep apnea	5.0 (3.9 - 6.3)	10.8
Arthralgia	Colonic diverticula	4.8 (3.0 - 7.6)	4.4
Hypertension	Sleep apnea	4.0 (3.3 - 4.8)	6.7
Arthralgia	Metabolic disorder	3.6 (2.9 - 4.3)	5.1
Hypertension	Fatigue	3.4 (2.8 - 4.0)	4.3
Arthralgia	Fatigue	3.4 (2.7 - 4.1)	4.7
Arthritis	Arthralgia	3.0 (2.5 - 3.5)	4.7
Arthritis	Hypertension	3.0 (2.5 - 3.6)	4.3
Hypertension	Metabolic disorder	2.9 (2.5 - 3.2)	4.7
Arthralgia	Hypertension	2.8 (2.4 - 3.2)	3.2

[a] Relative risk of the selected combination of conditions for acromegaly vs. non-acromegaly patients.
[b] The calculation of expected RR for conditions 1 & 2 assumes independence between risks of individual conditions.

Figure 1. Top 10 relative risks of selected dyad combinations with 95% confidence intervals*

*Upper bounds >20 truncated
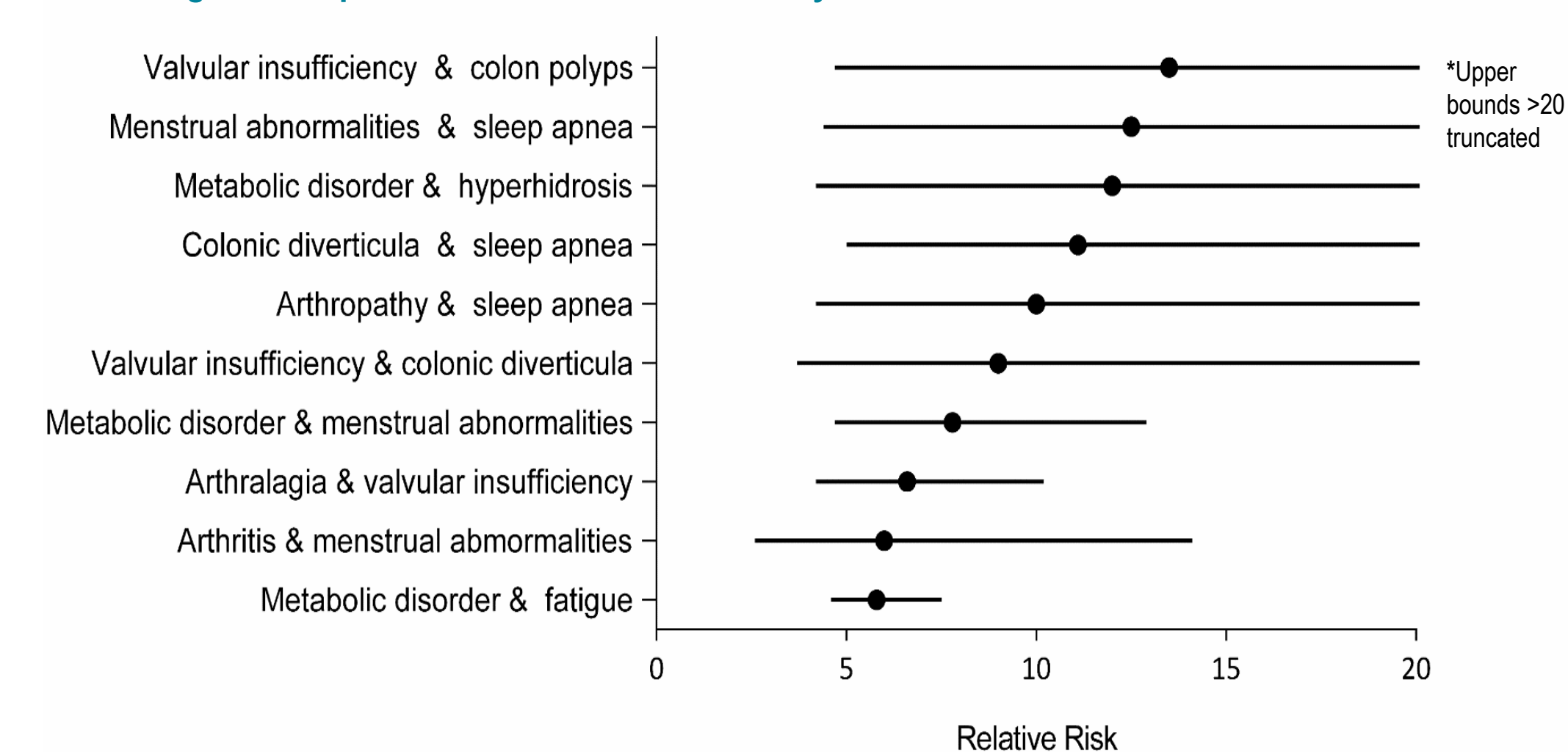
Selected Dyads of Conditions (cont.)

- The highest RRs, which exceeded expected, were for valvular insufficiency + colon polyps (RR=13.5; **Table 2** & **Figure 1**); menstrual abnormalities + sleep apnea (RR=12.5); metabolic disorder + hyperhidrosis (RR=12.0); colonic diverticula + sleep apnea (RR=11.1); and arthropathy + sleep apnea (RR=10.0).
- Replication using the validation dataset showed similar RR direction and size.

LIMITATIONS

- Results may not be generalizable to uninsured individuals.
- Use of ICD-9 codes may have led to misclassification (i.e., overreporting) of cases in our study due to rarity of the disease.[3]

CONCLUSIONS

- Analysis using large claims databases revealed several dyads (e.g., sleep apnea in the presence of menstrual abnormalities, colon diverticula, or arthropathy; and metabolic disorder in the presence of hyperhidrosis) that were many times more likely to occur among acromegaly patients, with RRs from 10 to 13.5.
- The presence of high-risk dyad combinations of clinical conditions could serve as potential markers for physicians to consider a diagnosis of acromegaly.
- Our findings may be useful in developing clinical screening tools to assist physicians in identifying patients having conditions possibly associated with acromegaly for early diagnostic testing.
- Future studies should examine the presence of high-risk dyad combinations in acromegaly cases prior to the time of diagnosis to determine their predictive value.

References
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