Predictive values of diagnostic codes for identifying serious hypocalcemia and dermatologic adverse events among women with postmenopausal osteoporosis in a commercial health plan database

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Abstract

Background: Post-marketing safety studies of medicines often rely on administrative claims databases to identify adverse outcomes following drug exposure. Valid ascertainment of outcomes is essential for accurate results. We aim to quantify the validity of diagnostic codes for serious hypocalcemia and dermatologic adverse events from insurance claims data among women with postmenopausal osteoporosis (PMO).

Methods: We identified potential cases of serious hypocalcemia and dermatologic events through ICD-9 diagnosis codes among women with PMO within claims from a large US healthcare insurer (June 2005-May 2010). A physician adjudicated potential hypocalcemic and dermatologic events identified from the primary position on emergency department (ED) or inpatient claims through medical record review. Positive predictive values (PPVs) and 95% confidence intervals (CIs) quantified the fraction of potential cases that were confirmed.

Results: Among 165,729 patients with PMO, medical charts were obtained for 40 of 55 (73%) potential hypocalcemia cases; 16 were confirmed (PPV 40%, 95% CI 25–57%). The PPV was higher for ED than inpatient claims (82 vs. 24%). Among 265 potential dermatologic events (primarily urticaria or rash), we obtained 184 (69%) charts and confirmed 128 (PPV 70%, 95% CI 62–76%). The PPV was higher for ED than inpatient claims (77 vs. 39%).

Conclusion: Diagnostic codes for hypocalcemia and dermatologic events may be sufficient to identify events giving rise to emergency care, but are less accurate for identifying events within hospitalizations.

Keywords: Administrative data, Dermatologic events, Hypocalcemia, Positive predictive value, Postmenopausal osteoporosis

Background

Osteoporosis, a condition characterized by loss of bone mass and increased risk of fracture, affects approximately 10 million individuals in the United States (US) [1]. Approximately 30% of postmenopausal Caucasian women have osteoporosis; their lifetime fracture risk is estimated as 40% [2]. Treatment includes abaloparatide, bisphosphonates, calcitonin, denosumab, raloxifene, and teriparatide, some of which have been linked with increased risk of hypocalcemia and adverse dermatologic events [3–7]. Post-marketing safety studies of medicines often rely on administrative claims databases to identify adverse outcomes following drug exposure [8–11]. Valid ascertainment of outcomes is essential for accurate results. Yet, the accuracy of identifying hypocalcemia and adverse dermatologic events, especially the more serious events, using claims-identified codes is not well described.

We conducted a study to assess the validity of diagnostic codes in claims data for hypocalcemia and dermatologic events, as compared with medical record confirmation of
events, among a population of women with postmeno-
pausal osteoporosis (PMO).

Methods
Data source
This observational study was a retrospective analysis of
medical and pharmacy claims data that are part of the
Optum Research Database (ORD), a proprietary research
database built from provider, facility, and pharmacy
claims of a large US health insurer affiliated with
Optum. The individuals covered by this health insurance
are geographically diverse, and represent 3–4% of the
US population.

There was no active enrollment or active follow-up of
patients, and no data were directly collected from
patients. The New England Institutional Review Board
provided oversight during the conduct of this study and
its Privacy Board granted a Waiver of Authorization for
linkage of claims and medical records.

Study population
The population included women with PMO who had
medical and pharmacy coverage between June 2005 and
May 2010. Women who were postmenopausal (age
55 years or older) and had diagnosis or treatment codes
indicative of osteoporosis or osteoporotic fracture were
eligible for the PMO population [12]. A list of relevant
codes is provided in an Additional file 1: Table S1. We
required at minimum 6 months of continuous enroll-
ment in the health plan preceding the first code indicat-
ing PMO (baseline period). We used data from the
baseline period to determine cohort eligibility and to
characterize baseline attributes for study members.

Identification of potential outcomes through claims data
Potential events were identified through diagnosis codes
for hypocalcemia (ICD-9 275.41) or dermatologic ad-
verse events (bullous dermatoses [ICD-9 694.xx], ery-
thematosus events [ICD-9 695.1x, 695.5x], or urticaria or
rash [ICD-9 708.x, 782.1]) associated with an emergency
department (ED) visit or inpatient hospitalization. To
capture serious events, we excluded potential cases re-
corded outside of the ED or inpatient setting, and add-
tionally included only events with codes recorded in the
first (primary) position on the claim. Within our data
system, the primary diagnostic code on hospitalization-
associated claims represents the principal diagnosis, the
condition established after study to be chiefly respon-
sible for the admission [13].

Case confirmation through medical record review
We sought medical records for all hypocalcemia, bullous
dermatoses, and erythematous events and for a random
sample of urticarial or rash events identified from the
claims. A chronological list of claims for each of the po-
tential cases was reviewed to determine the site of med-
icare most likely to yield the necessary information
for case confirmation. A physician blinded to the pa-
tients’ osteoporosis medication use reviewed the medical
records and classified each potential case as: definite
case; definite non-case; or insufficient information. Def-
ite cases of hypocalcemia were identified based on the
designation of hypocalcemia diagnosis by either the ad-
mitting or consulting physician, with confirmation
through the lab result that triggered the diagnosis. For
both hypocalcemia and dermatologic events, a definite
case classification also required attribution of the event
as the leading cause for the hospitalization or ED visit
(non-incidental cases).

Statistical analysis
We calculated the positive predictive value (PPV) and
associated 95% confidence interval (CI) among potential
cases for which we obtained a medical record. The PPV
was defined as the proportion of potential cases classified
as definite cases—calculated overall, and for dermatologic
events, by subgroups (bullous dermatoses, erythematous
events, and urticaria/rash). CIs were calculated using the
exact binomial Wilson method [14]. We stratified the re-
sults by site of care, and, in a secondary analysis, by pro-
vider specialty. To evaluate the importance of our
requirement that events led to the hospitalization or ED
visit, we included both non-incidental and incidental cases
in the numerator of PPV estimates in a sensitivity analysis.
In this case, incidental events were those confirmed
events based on medical record review but listed within the med-
cal record as a secondary reason for the hospitalization or
ED visit.

Results
The population consisted of 165,729 women with PMO,
the majority of whom were between 55 and 64 years of
age, and white, reflecting the underlying population of
the database (Table 1). We sought charts for 55 patients
with qualifying claims for hypocalcemia, for which 40
(73%) charts were received. Sixteen potential cases were
confirmed hypocalcemia leading to hospitalization or ED
visit, yielding a PPV of 40.0% (95% CI 24.9–56.7%)
(Table 2). One potential case had insufficient information
for adjudication. Claims associated with ED setting (PPV
81.8%, 95% CI 48.2–97.7%) performed better than those
from inpatient setting (PPV 24.1%, 95% CI 10.3–43.5%).
The PPV for hypocalcemia was higher for claims
associated with emergency medicine (PPV 54.2%, 95% CI
32.8–74.4%) as compared with other provider specialties.
The inclusion of incidental hypocalcemia events yielded a
higher PPV (70.0%, 95% CI 54.6–81.9%).
Medical records were sought for a random 265 of 441 potential dermatologic adverse events identified from the database (6 bullous, 15 erythematous, 247 urticaria/rash and 3 with multiple codes); 184 (69%) charts were received (all had sufficient information for adjudication). The physician confirmed 128 as dermatologic events (PPV 69.6%, 95% CI 62.4–76.1%) (Table 2). PPVs varied across subtypes of dermatologic events (highest for urticaria/rash [PPV 70.5%, 95% CI 63.1–77.2%]) and healthcare setting (highest for ED [PPV 77.0%, 95% CI 69.4–83.5%]). Additionally, the PPV was higher for claims associated with emergency medicine (PPV 78.1%, 95% CI 70.2–84.7%) relative to other provider specialties. The inclusion of incidental dermatologic adverse events had little impact (PPV 74.5%, 95% CI 67.7–80.2%).

### Discussion

In this nationwide, observational study of women with PMO, the performance of diagnosis codes in identifying hypocalcemia and dermatologic adverse events from health insurance claims data varied across settings, and by provider specialty. Our definition of hypocalcemia (as the primary reason for obtaining ED or inpatient care) yielded a PPV of 40%, and for dermatologic adverse events, a PPV of 70%. The inclusion of incidental cases increased the PPV of hypocalcemia appreciably, suggesting that secondary hypocalcemia may be recorded in the primary position on claims. Incidental cases were infrequent for dermatologic adverse events, possibly because these events generally were the primary reason for the patients’ care. With both outcomes, the diagnosis codes from ED claims were more accurate than inpatient claims. Serious hypocalcemia and dermatologic adverse events may be treated and resolved within the ED without requiring hospital admission, and if hospitalization does occur, these outcomes—hypocalcemia in particular—may be considered a secondary concern.

There are few published data for comparison. Strom et al. reported that within Medicaid claims, 60.9% of the erythematous events captured through presence of ICD-9 695.1 (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) were later confirmed as true cases [15]. Within a health plan database, Chan et al. reported that the presence of a discharge diagnosis of erythema multiforme yielded a PPV of 60.7% [16]. These are similar to our PPV finding of 56 to 67% (including incidental cases) for serious erythematous events, which also included ICD-9 695.5 (exfoliation due to erythematous conditions).

Historically, 70 to 80% of medical records requested by our research group (and similar institutions) are obtained [17, 18]. In this study, as expected, our retrieval rate was at the lower end of this spectrum as we sought medical records only from the principal site of care. This choice arose from the study objective to validate outcomes associated with a specific medical claim, rather than to confirm the presence of an outcome. While our lower retrieval rate decreased the precision of the PPVs, leading to broader confidence intervals, it likely did not bias the PPVs estimates, unless the chart retrieval rate was somehow differential with respect to the true case status. For example, if hospitals were more likely to provide charts for true cases of hypocalcemia, our PPV estimates would be biased toward 100%. However, this scenario seems unlikely. With other study objectives, it

### Table 1
Baseline characteristics of PMO study population, June 2005 – May 2010

| Characteristics                  | Number of patients (%) |
|----------------------------------|------------------------|
| **N = 165,729**                  |                        |
| **Age (years)**                  |                        |
| 55 to 64                         | 130,344 (78.6)         |
| 65 to 69                         | 17,348 (10.5)          |
| 70 to 74                         | 7966 (48)              |
| ≥ 75                             | 10,071 (6.1)           |
| **Race**                         |                        |
| Asian                            | 3898 (2.4)             |
| Caucasian                        | 123,788 (74.7)         |
| Hispanic                         | 10,131 (6.1)           |
| Black                            | 12,579 (7.6)           |
| Other                            | 1200 (0.7)             |
| Unknown                          | 14,077 (8.5)           |
| **Geographic region**            |                        |
| Northeast                        | 14,124 (8.5)           |
| Midwest                          | 35,746 (21.6)          |
| South                            | 98,519 (59.4)          |
| West                             | 16,965 (10.2)          |
| Unknown                          | 375 (0.2)              |
| **Calendar year of cohort entry**|                        |
| 2005                             | 49,311 (29.8)          |
| 2006                             | 34,899 (21.1)          |
| 2007                             | 26,828 (16.2)          |
| 2008                             | 28,508 (17.2)          |
| 2009                             | 20,390 (12.3)          |
| 2010                             | 5793 (3.5)             |
| **Usage of healthcare facilities**|                      |
| Patients with at least one physician office/outpatient visit | 154,648 (93.3)         |
| Patients with at least one emergency room visit | 28,381 (17.1)         |
| Patients with at least one hospitalization | 11,472 (6.9)          |

**Abbreviation:** PMO Post-Menopausal Osteoporosis
| Event of interest | Charts requested | Charts obtained | Confirmed cases | PPV % | 95% CI |
|------------------|------------------|-----------------|----------------|--------|--------|
|                  | N               | N              | n              | PPV % | 95% CI |
| Hypocalcemia     |                 |                |                |        |        |
| Overall          | 55              | 40             | 16             | (24.9–56.7) |
| By site of care  |                 |                |                |        |        |
| Emergency department | 12          | 11             | 9              | 81.8   | (48.2–97.7) |
| Hospital         | 43              | 29             | 7              | 24.1   | (10.3–43.5) |
| By provider specialty |           |                |                |        |        |
| Emergency medicine | 31            | 24             | 13             | 54.2   | (32.8–74.4) |
| Internal medicine | 33              | 21             | 5              | 23.8   | (8.2–47.2) |
| Cardiology       | 26              | 16             | 3              | 18.8   | (4.0–45.6) |
| Other specialties | 44              | 30             | 8              | 26.7   | (12.3–45.9) |
| With inclusion of incidental cases | 55          | 40             | 28             | 70.0   | (54.6–81.9) |
| Dermatologic adverse events |        |                |                |        |        |
| Overall          | 265 f           | 184            | 128            | 69.6   | (62.4–76.1) |
| Bullous dermatoses | 6                | 3             | 1              | 33.3   | (0.8–90.6) |
| Erythematous event | 15            | 9              | 5              | 55.6   | (21.2–86.3) |
| Urticaria or rash | 247               | 173           | 122            | 70.5   | (63.1–77.2) |
| By site of care  |                 |                |                |        |        |
| Emergency department |           |                |                |        |        |
| Overall          | 214             | 148            | 114            | 77.0   | (69.4–83.5) |
| Bullous dermatoses | 1                | 0             | 0              | –      | –      |
| Erythematous event | 7                | 3             | 2              | 66.7   | (9.4–99.2) |
| Urticaria or rash | 207               | 145           | 112            | 77.2   | (69.5–83.8) |
| Hospital         |                 |                |                |        |        |
| Overall          | 51              | 36             | 14             | 38.9   | (23.1–56.5) |
| Bullous dermatoses | 5                | 3             | 1              | 33.3   | (0.8–90.6) |
| Erythematous event | 8                | 6             | 3              | 50.0   | (11.8–88.2) |
| Urticaria or rash | 40               | 28             | 10             | 35.7   | (18.6–55.9) |
| By provider specialty |           |                |                |        |        |
| Emergency medicine |           |                |                |        |        |
| Overall          | 192             | 137            | 107            | 78.1   | (70.2–84.7) |
| Bullous dermatoses | 9                | 6             | 4              | 66.7   | (22.3–95.7) |
| Erythematous event | 3                | 2             | 1              | 50.0   | (1.3–98.7) |
| Urticaria or rash | 181              | 129            | 102            | 79.1   | (71.0–85.7) |
| Internal medicine |                 |                |                |        |        |
| Overall          | 43              | 30             | 14             | 46.7   | (28.3–65.7) |
| Bullous dermatoses | 5                | 4             | 2              | 50.0   | (6.8–93.2) |
| Erythematous event | 3                | 2             | 1              | 50.0   | (1.3–98.7) |
| Urticaria or rash | 37               | 25             | 11             | 44.0   | (24.4–65.1) |
| Dermatology      |                 |                |                |        |        |
| Overall          | 21              | 13             | 5              | 38.5   | (13.9–68.4) |
| Bullous dermatoses | 7                | 6             | 3              | 50.0   | (11.8–88.2) |
| Erythematous event | 3                | 1             | 0              | 0.0    | (0.0–97.5) |
is generally feasible to seek charts from multiple providers or institutions (e.g., a dermatologist and a hospital) to increase the fraction of events for which at least one medical record is available.

In this study, we had expected that limiting our algorithm to the first-position diagnoses on claims would increase the PPV for capturing serious occurrences of adverse events that were the primary reason for seeking care. However, we found that clinically incidental or secondary events are also captured through diagnosis codes recorded in the primary position. Further, it is important to note that outcomes leading to hospitalization or ED visits may have had ICD-9 codes recorded in a secondary position on claims. These cases were not counted in this study, and thus, incidence derived with these code sets will be underestimated.

This study was conducted in a US commercially-insured population which, on average, tend to be slightly younger than the US general population. While we expect the results of this study to be generalizable to other insured populations, caution must be taken if there are differences in coding standards for reimbursement for hypocalcemia or dermatologic adverse events across insurers. Further, as PPVs vary according to disease prevalence, our PPVs may underestimate those observed in populations with a higher prevalence of hypocalcemia and/or dermatologic events than our study population, and overestimate those observed in populations with lower prevalence of these conditions than our study population. This highlights the need to assess the performance of case-identification algorithms within specific populations of interest. Lastly, we recognize that additional work is needed to assess the performance of algorithms for identifying other outcomes of interest that are associated with the use of osteoporosis medication, including osteonecrosis of the jaw, and atypical femur fractures.

**Conclusion**

Our results suggest that the current algorithms to identify serious hypocalcemia and dermatologic adverse events are moderately accurate for events leading to an ED visit (PPV 81.8% for hypocalcemia and PPV 77.0% for dermatologic adverse events) and has lower accuracy for events leading to hospitalization. In certain scenarios, estimates derived from the current claims definitions may be insufficient, and algorithms that include other components of insurance claims data should be explored.
to further refine the algorithm. Alternatively, the outcome definitions could be widened to include all occurrences of the events that result in healthcare services.

Additional file

Additional file 1: Table S1. Algorithm for identifying post-menopausal osteoporosis. (DOCX 14 kb)

Abbreviations

CI: Confidence interval; ED: Emergency department; ORD: Optum Research Database; PWO: Postmenopausal osteoporosis; PPVs: Positive predictive values

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Availability of data and materials

 Portions of the administrative claims data that support the findings of this study are available through the purchase of a data license and appropriate permissions from Optum. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Individual patient data are not available due to privacy restrictions.

Authors’ contributions

FW made substantial contributions to the conception and design, analysis and interpretation of data, and had been involved in drafting the manuscript and revising it critically for important intellectual content. FX made substantial contributions to the conception and design, and interpretation of data, and had been involved in revising the manuscript critically for important intellectual content. DY made substantial contributions to the interpretation of data, and had been involved in revising the manuscript critically for important intellectual content. EN made substantial contributions to the conception and design, analysis and interpretation of data, and had been involved in revising the manuscript critically for important intellectual content. CC made substantial contributions to the analysis of data, and had been involved in drafting the manuscript critically for important intellectual content. DY made substantial contributions to the conception and design, and interpretation of data, and had been involved in revising the manuscript critically for important intellectual content. CC made substantial contributions to the interpretation of data, and had been involved in revising the manuscript critically for important intellectual content. DD made substantial contributions to the conception and design, and interpretation of data, and had been involved in revising the manuscript critically for important intellectual content.

Ethics approval and consent to participate

This study was conducted using secondary data. There was no active enrollment or active follow-up of patients, and no data were directly collected from patients. The New England Institutional Review Board provided oversight during the conduct of this study and its Privacy Board granted a Waiver of Authorization for linkage of claims and medical records.

Consent for publication

Not applicable

Competing interests

FW, DD, YD, and EN are employees of Optum Epidemiology. FX and CC are employees of Amgen, Inc.

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