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Pseudogout among Patients Fulfilling a Billing Code Algorithm for Calcium Pyrophosphate Deposition Disease

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Abstract

Objective—To test the performance of a billing claims-based calcium pyrophosphate deposition disease (CPPD) algorithm for identifying pseudogout.

Methods—We applied a published CPPD algorithm at an academic institution and randomly selected 100 patients for electronic medical record review for 3 phenotypes: 1) definite/probable CPPD, 2) definite/probable pseudogout; 3) definite pseudogout. Clinical data were recorded and positive predictive value (PPV) (95% CI) for each phenotype was calculated. We then modified the published algorithm to require 1 of 4 relevant terms (“pseudogout”, “calcium pyrophosphate crystals”, “CPPD”, or “chondrocalcinosis”) through automated text searching in clinical notes, and re-calculated PPVs. To estimate the percentage of pseudogout patients not identified by the published algorithm, we reviewed a random sample of 50 patients with 1 of 4 relevant terms in clinical notes who did not fulfill the published algorithm.

Results—Among patients fulfilling the published algorithm, 68% had 1 of 3 phenotypes. The published algorithm had PPV 24.0% (95% CI 19.3–28.7%) for definite/probable pseudogout and 18.0% (95% CI 14.5–21.5%) for definite pseudogout. Requiring 1 of 4 relevant terms in clinical notes increased PPV to 33.3% (95% CI 26.8–39.8%) for definite/probable pseudogout and 24.6% (95% CI 19.8–29.4%) for definite pseudogout. Among patients not fulfilling the published algorithm, 16.0% had definite/probable pseudogout and 6.0% had definite pseudogout.

Conclusion—A billing code-based CPPD algorithm had low PPV for identifying pseudogout. Adding text searching modestly enhanced the PPV, though it remained low. These findings highlight the need for improved approaches to identify pseudogout to facilitate epidemiologic studies.

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ETHICAL APPROVAL: For this type of study formal consent is not required.

Keywords

pseudogout; calcium pyrophosphate; CPPD; algorithm

INTRODUCTION

Pseudogout is the most inflammatory phenotype of calcium pyrophosphate deposition disease (CPPD), causing joint pain, swelling and limited function [1]. Pseudogout is clinically defined by the presence of synovial fluid calcium pyrophosphate (CPP) crystals on polarized microscopy in the context of synovitis [2]. Ryan and McCarty proposed criteria to clinically diagnose CPPD [3], but CPPD classification criteria for use in research studies do not exist. The European League Against Rheumatism (EULAR) recently proposed terminology for a spectrum of CPPD phenotypes including asymptomatic radiographic chondrocalcinosis, osteoarthritis with chondrocalcinosis, acute CPP crystal arthritis (pseudogout) and chronic CPP crystal arthritis [4].

Pseudogout is a common inflammatory arthritis without targeted treatment options. Studying pseudogout risk factors and outcomes has been difficult due to a paucity of cohorts or validated algorithms to identify patients with pseudogout. A limited number of epidemiologic studies have focused on pseudogout specifically, rather than a broader definition of CPPD [5, 6]. Importantly, there are no billing codes specifically for pseudogout in the ICD-9 or ICD-10 system. However, a billing code-based algorithm for CPPD, which includes pseudogout, was developed using Veterans' Administration (VA) Medical Center data [7]. The algorithm was designed to identify "definite or probable CPPD" based on Ryan and McCarty's diagnostic criteria [3], defined as joint pain plus either CPP crystals in synovial fluid or radiographic chondrocalcinosis, or both. Thus, the focus of the algorithm was on a broader definition of joint pain and chondrocalcinosis rather than the specific phenotype of pseudogout.

In an effort to identify patients with pseudogout, we tested the performance of the published CPPD algorithm in identifying pseudogout patients using electronic medical record (EMR) data at an independent academic institution. Furthermore, we assessed whether using information from the text in clinical notes could improve the performance of the existing billing code algorithm. This work was presented in an abstract at the American College of Rheumatology 2017 Annual Meeting.[8]

METHODS**Study Population**

We studied >7 million patients followed largely at academic tertiary care centers. Patient data are stored in the Partners Healthcare Research Patient Data Registry (RPDR), which contains detailed clinical and administrative electronic medical record (EMR) data from the inpatient, outpatient and emergency settings. The RPDR includes structured data, such as prescriptions, billing codes, and laboratory results, and unstructured data such as text in clinical notes. Investigators have the ability to search for specific terms or phrases within

clinical notes in the RPDR using a string text search tool. This tool allows the investigator to search for one or more phrases of interest and to specify the type of clinical note to be searched (e.g. ambulatory visit notes, discharge summaries). RPDR queries can include both structured data fields and text searching in clinical notes.

Following published methods we applied the published CPPD algorithm to adults age 18 years with 1 encounter in the RPDR, 1/1/2015–12/31/2016. The published CPPD algorithm includes 1 ICD-9 code: 712.1–712.39 (chondrocalcinosis due to dicalcium phosphate crystals, due to pyrophosphate crystals, or cause unspecified) or 275.49 (other disorders of calcium metabolism) [7]. Among patients fulfilling the published algorithm, we randomly selected a sample of 100 subjects and reviewed their EMR data from the date of first qualifying ICD-9 code through 5/1/2017. This study was approved by the Partners Healthcare Institutional Review Board (IRB) on 2 September 2016, as Protocol #2016P001892. Informed consent was not required by the IRB for this study using medical record data.

Data Collection

We evaluated each record for three arthritis phenotypes: 1) “definite or probable CPPD” as defined in the published CPPD algorithm [7], 2) definite or probable pseudogout (modified from EULAR) [4], and 3) definite (crystal-proven) pseudogout (Table 1). We recorded demographics and clinical data including joint pain, synovitis (defined as joint pain, swelling, and tenderness), diagnoses, chondrocalcinosis on x-ray, and synovial fluid aspirate results when available. Among patients meeting the definition of definite pseudogout or definite or probable pseudogout, we recorded affected joints and medical treatments.

Modification of the Published CPPD Algorithm to Include Text Searching

Within the sample of patients fulfilling the published CPPD algorithm, we further refined the RPDR query to include text searching for 1 of four terms related to pseudogout: “pseudogout”, “calcium pyrophosphate crystals”, “CPPD”, or “chondrocalcinosis”. The query was performed among ambulatory visit notes and discharge summaries, including Emergency Department discharge summaries.

Estimation of Pseudogout Cases Missed by the Published CPPD Algorithm

We estimated the percentage of patients without any of the four ICD-9 codes (275.49, 712.1, 712.2, 712.3) who met the study definitions of pseudogout. To do so, we queried the RPDR for patients who never had any of these ICD-9 billing codes documented, and required that a text search of ambulatory visit notes and discharge summaries contained 1 of the four above-mentioned terms related to pseudogout. We randomly selected 50 of these patients and reviewed the EMR from the date of first EMR encounter through 12/21/2017 for each of the two pseudogout phenotypes.

Statistical Analysis

We calculated PPV and 95% confidence intervals (CI) for each of the three arthritis phenotypes in the sample of patients fulfilling the published CPPD algorithm. Two patients did not have clinical notes; both had pathology reports documenting tumoral calcinosis,

billed under ICD-9 275.49. We recorded clinical data for the 98 patients with clinical notes and calculated PPV among all 100 patients. After modifying the published CPPD algorithm to additionally include text searching, we calculated PPV (95% CI), negative predictive value (NPV) (95% CI), and sensitivity (95% CI) for each of the three arthritis phenotypes. Among patients without any pertinent ICD-9 codes but with a positive text search for pertinent terms, we calculated the percentage and 95% CI with each pseudogout phenotype to estimate the percentage of pseudogout cases missed by billing codes. Analyses were performed using SAS v9.4 (SAS Institute, Cary, N.C.).

RESULTS

Characteristics of Patients Fulfilling the Published CPPD Algorithm

We identified 1,236 patients fulfilling the published CPPD algorithm during the study period. In our sample of patients fulfilling the published algorithm, 68% had at least one of the three arthritis phenotypes by EMR review. Median age was 70.0 years (range 25.0–98.0 years) and more than half were female (Table 2). Osteoarthritis was documented in clinical notes or structured problem lists for 74.5% of patients. Joint pain was reported by 87.7% of patients and 34.7% had synovitis documented. More than 80% of patients were evaluated by a rheumatologist or orthopedic surgeon, and osteoarthritis and pseudogout (described as possible, probable, or definite pseudogout) were the most commonly documented explanations for joint symptoms in clinical notes. Rheumatologists and orthopedic surgeons made other diagnoses in 22% of patients including meniscal tear, calcific tendinitis, calciphylaxis, and joint trauma. X-ray of at least one joint was performed in 93.9% of patients and chondrocalcinosis was present in 60.9% of imaged joints. Arthrocentesis was performed in 25.5% of patients; synovial fluid from 18 patients (72.0% of aspirates) revealed CPP crystals.

Among patients who fulfilled the published CPPD algorithm, 24.0% had definite or probable pseudogout and 18.0% had pseudogout. All patients meeting these definitions had synovitis as required by our study definitions (Table 1). Pseudogout patients tended to be younger and more racially diverse (though still majority White) compared to the entire sample. Osteoarthritis was present in similar portions of pseudogout patients and the entire sample. Joint x-rays revealed chondrocalcinosis in the affected joint in less than 50% of the sample.

Among patients with definite pseudogout, treatments for the first documented episode included non-steroidal anti-inflammatory drugs (37.5%), oral steroids (37.5%), intra-articular steroid injection (25.0%), and colchicine (12.5%). Sixteen of 18 patients were evaluated by a rheumatologist or orthopedic surgeon; the physician's diagnosis was "pseudogout" in 15 of 16 and "CPPD" for the remaining patient. Among those with x-rays performed, fewer than 20% of affected joints had chondrocalcinosis.

Performance of Algorithms

Among patients who fulfilled the published CPPD algorithm, 68.0% met the definition of definite or probable CPPD (PPV 68.0%, 95% CI 54.7–81.3%) (Table 3). The published

CPPD algorithm had PPV 24.0% (95% CI 19.3–28.7%) for definite or probable pseudogout and 18.0% (95% CI 14.5–21.5%) for definite pseudogout.

When we required 1 of four terms in clinical notes in addition to 1 of four ICD-9 codes, the PPV for each of the three arthritis phenotypes increased (Table 3). However, the percentage of patients that had definite pseudogout was still less than 25%. NPV was 96.8% (95% CI 77.8–100.0%) for definite or probable pseudogout and also for definite pseudogout. Requiring text searching for 1 of four terms in addition to 1 of four ICD-9 codes was extremely sensitive for pseudogout, identifying 95.8% of patients with definite or probable pseudogout and 94.4% with definite pseudogout.

Estimation of Pseudogout Cases Missed by the Published CPPD Algorithm

In the Partners Healthcare RPDR, 5,470 patients had ambulatory visit notes or discharge summaries containing 1 of the four relevant terms and never had any of the four relevant ICD-9 codes billed. In our sample of these patients, 16.0% fulfilled the definition of definite or probable pseudogout and 6.0% had definite pseudogout.

DISCUSSION

Among patients fulfilling a published billing code algorithm for CPPD, 68.0% had at least one of three CPPD or pseudogout phenotypes by EMR review. The published algorithm had a low PPV for pseudogout: 24.0% of patients fulfilled a definition of definite or probable pseudogout, and only 18.0% of patients had definite (crystal-proven) pseudogout. We further assessed whether including information from narrative data could improve the algorithm and found a modest improvement in PPV for pseudogout from 24.0% to 33.3% for definite or probable pseudogout and from 18.0% to 24.6% for definite pseudogout. The string text search was 94.4% sensitive for definite pseudogout.

The PPV for definite or probable CPPD, which the published CPPD algorithm was designed to identify, was lower in our academic medical center (68%) than in the VA Medical Center where it was developed (91%) [7]. It is possible that the difference is due to the difference in demographics and the range of diagnoses for which the four ICD-9 billing codes were applied. Patients who fulfilled the published CPPD algorithm in our tertiary care medical center were predominantly women, and a number had non-arthritis calcium disorders including calciphylaxis, nephrocalcinosis, and tumoral calcinosis billed under ICD-9 code 275.49 (other disorders of calcium metabolism). The CPPD algorithm was developed in a predominantly male study population at the Milwaukee VA Medical Center, and all patients had arthritis upon medical record review [7]. Pseudogout is a subtype of CPPD, so when we added text searching for terms related to pseudogout, we also increased the PPV for CPPD from 68% to 74%. To further improve the PPV for CPPD in our medical center, possible methods include: adding ICD-9 and ICD-10 codes for “inflammatory arthritis”, requiring >1 ICD-9 code (712.1, 712.2, 712.3, 275.49) rather than just 1 code, or attempting to exclude patients with calciphylaxis (billed under ICD-9 275.49) by excluding patients with ICD-9 codes for end-stage renal disease (ESRD). Excluding patients with ESRD would likely lower the sensitivity for CPPD while improving PPV.

Based on prior studies, we may infer that up to 40% of patients with pseudogout lack chondrocalcinosis, raising concerns about potential underestimation of pseudogout through these codes [2]. Among patients with definite or probable pseudogout, only 18.8% had chondrocalcinosis in the affected joint. The low prevalence of chondrocalcinosis in the affected joint may reflect low utilization of x-rays in evaluating acute synovitis or absence of chondrocalcinosis when an x-ray was obtained. Relying on billing codes for chondrocalcinosis to identify pseudogout thus underestimates the number of afflicted patients. The CPPD algorithm included a billing code for “other disorders of calcium metabolism” in addition to the chondrocalcinosis codes. However, in a sample of patients that never had any of the four pertinent ICD-9 codes we demonstrated that using these four billing codes as a screening tool for pseudogout was suboptimal.

The aim of our study was to test the ability of a published CPPD algorithm to accurately identify pseudogout, rather than to validate the published algorithm. Our study found that few patients fulfilling the published CPPD algorithm have pseudogout, and that the algorithm does not capture all patients with pseudogout. Pseudogout prevalence in the general population has not been well-characterized. Inclusion of as many pseudogout cases as possible in epidemiologic studies is necessary to most accurately characterize risk factors for and outcomes of patients with this under-studied disease.

Given the limitations of billing code-based algorithms for identifying pseudogout, we anticipate that methods incorporating various types of EMR data will enable more accurate identification of this phenotype for research purposes. An algorithm that accurately identifies pseudogout patients in the EMR would allow investigators to study risk factors for and long-term outcomes in pseudogout patients, and is not intended to make a clinical diagnosis of pseudogout. This is akin to the purpose of ACR/EULAR classification criteria for gout, rheumatoid arthritis, and other diseases, which identify patients that can be included in research studies and are not intended for clinical diagnosis [9, 10]. Text searching modestly improved the algorithm’s PPV for definite or probable pseudogout from 24.0% to 33.3%, allowing for identification of additional patients with pseudogout with good sensitivity. Natural language processing (NLP) is a computational method that can extract information from unstructured data—such as text from clinical notes and radiology reports, which traditionally require human interpretation. NLP processes the unstructured data into concepts, e.g. synovitis, that can be used for algorithm development together with structured EMR data such as laboratory results, billing codes, and prescriptions [11]. Given our preliminary results using a string text search, NLP may be particularly useful for helping to identify pseudogout since there is no specific billing code for the disease [11].

Our study had several limitations including small sample size, leading to wide confidence intervals for our estimates of PPV and sensitivity. Nonetheless we were able to demonstrate that the published CPPD algorithm had low PPV for pseudogout. We retrospectively reviewed EMR data collected in routine clinical practice, meaning that the type and amount of data available for each patient varied; for example, a small minority of patients did not have joint x-rays. However, we were able to gather detailed data for each patient and determine whether they met our study definitions for pseudogout. We investigated two pseudogout phenotypes, reflecting the gold standard clinical diagnosis of pseudogout (i.e.

synovial fluid aspiration demonstrating CPP crystals) and a more inclusive definition that does not require synovial fluid aspiration based on EULAR recommendations [4]. Both pseudogout phenotypes required documentation of synovitis (Table 1), which may not be clearly documented in clinical notes and raises the possibility of under-ascertainment of this disease. In attempt to identify patients with convincing evidence for pseudogout we decided to require synovitis in our definitions. Synovial fluid aspiration is under-utilized in gout; <5% of gout diagnoses made in community-based settings are crystal-proven [12]. Pseudogout often affects the wrist and ankle, joints that can be challenging to aspirate without imaging guidance, thus we expect that most pseudogout patients have not undergone synovial fluid aspiration. Future investigations of pseudogout epidemiology, utilizing NLP to most accurately identify patients using EMR data, would benefit from focusing on both the gold standard diagnosis as well as the broader, “real-world” definition of pseudogout.

CONCLUSIONS

A published billing-code based algorithm for CPPD had low PPV for identifying pseudogout in EMR data. Approaches which allow extraction of narrative data from text notes using NLP, is a promising approach to develop algorithms that can identify pseudogout patients with higher accuracy and sensitivity to facilitate epidemiologic studies of pseudogout.

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Table 1

CPPD and pseudogout phenotypes and definitions

CPPD phenotype	CPPD definition
Definite or probable CPPD [*]	Joint pain <u>and either</u> synovial fluid with calcium pyrophosphate crystals <u>or</u> chondrocalcinosis in <i>any</i> joint <u>or both</u>
Pseudogout phenotypes	Pseudogout definitions
Definite or probable pseudogout ⁺	Synovitis (pain, swelling and tenderness) in the affected joint <u>and either</u> synovial fluid with calcium pyrophosphate crystals <u>or</u> chondrocalcinosis in the <i>affected</i> joint <u>or both</u>
Definite pseudogout	Synovitis (pain, swelling and tenderness) in the affected joint <u>and</u> synovial fluid with calcium pyrophosphate crystals

^{*} Outcome used in the validated CPPD algorithm,[7] based on Ryan and McCarty's diagnostic criteria[1]

⁺ Modified from EULAR 2011 recommended CPPD terminology[4]

Table 2

Characteristics of patients identified by a published CPPD algorithm *

	All patients n=100	Definite or probable pseudogout [#] n=24	Definite pseudogout ^{##} n=18
Median age (range), years	70.0 (25.0–98.0)	70.5 (33.0–90.0)	65.0 (33.0–90.0)
Female	55.0	54.2	55.6
White	82.0	79.2	72.2
Osteoarthritis	74.5 ⁺	75.0	72.2
Joint pain	87.7 ⁺	100.0	100.0
Synovitis	34.7 ⁺	100.0	100.0
Rheumatologist or orthopedist evaluation	83.7 ⁺	87.5	88.9
Rheumatologist or orthopedist diagnosis ⁺⁺			
pseudogout	35.4	85.7	93.8
CPPD	9.8	9.5	6.3
osteoarthritis	37.8	4.8	0
gout	6.1	14.3	6.3
other	22.0	9.5	6.3
X-ray of any joint performed	93.9 ⁺	91.7	88.9
Chondrocalcinosis in any joint [^]	60.9	50.0	31.3
Chondrocalcinosis in painful joint [^]	54.3	40.9	18.8
Arthrocentesis performed	25.5 ⁺	83.3	100.0
Synovial fluid with CPP crystals [^]	72.0	90.0	100.0

Presented as percentage except when noted

* See reference [7]

⁺ Presented as percentage of 98 patients with clinical EMR data[#] Synovitis (pain, swelling and tenderness) in the affected joint and either synovial fluid with CPP crystals or chondrocalcinosis in the affected joint, or both^{##} Synovitis (pain, swelling and tenderness) in the affected joint and synovial fluid with CPP crystals⁺⁺ Presented as percentage of patients evaluated by a rheumatologist or orthopedist. Diagnoses recorded from clinical notes (not billing codes). More than 1 diagnosis possible per patient.[^] Presented as the percentage of patients that had the test performed

Table 3

Algorithm Performance for Identifying CPPD and Pseudogout

	CPPD Algorithm		CPPD Algorithm + Text Searching	
	PPV (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	Sensitivity (95% CI)
CPPD phenotype				
Definite or probable CPPD	68.0 (54.7–81.3)	n/a	73.9 (59.4–88.4)	75.0 (60.3–89.7)
Pseudogout phenotypes				
Definite or probable pseudogout	24.0 (19.3–28.7)	n/a	33.3 (26.8–39.8)	95.8 (77.0–100.0)
Definite pseudogout	18.0 (14.5–21.5)	n/a	24.6 (19.8–29.4)	94.4 (75.9–100.0)

All values are percentages. CPPD algorithm sensitivity not calculated because 100% of the study sample fulfilled the algorithm by design