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Review

A systematic review of validated methods for identifying patients with rheumatoid arthritis using administrative or claims data

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ABSTRACT

Purpose: To review the evidence supporting the validity of billing, procedural, or diagnosis code, or pharmacy claim-based algorithms used to identify patients with rheumatoid arthritis (RA) in administrative and claim databases.
Methods: We searched the MEDLINE database from 1991 to September 2012 using controlled vocabulary and key terms related to RA and reference lists of included studies were searched. Two investigators independently assessed the full text of studies against pre-determined inclusion criteria and extracted the data. Data collected included participant and algorithm characteristics.
Results: Nine studies reported validation of computer algorithms based on International Classification of Diseases (ICD) codes with or without free-text, medication use, laboratory data and the need for a diagnosis by a rheumatologist. These studies yielded positive predictive values (PPV) ranging from 34 to 97% to identify patients with RA. Higher PPVs were obtained with the use of at least two ICD and/or procedure codes (ICD-9 code 714 and others), the requirement of a prescription of a medication used to treat RA, or requirement of participation of a rheumatologist in patient care. For example, the PPV increased from 66 to 97% when the use of disease-modifying antirheumatic drugs and the presence of a positive rheumatoid factor were required.
Conclusions: There have been substantial efforts to propose and validate algorithms to identify patients with RA in automated databases. Algorithms that include more than one code and incorporate medications or laboratory data and/or required a diagnosis by a rheumatologist may increase the PPV.

Contents

Abbreviations: A, algorithm; ACR, American College of Rheumatology; AMI, acute myocardial infarction; ANA, antinuclear antibody; anti-TNF, anti-tumor necrosis factor; anti-CCP, anti-cyclic citrullinated peptide; CI, confidence interval; CD, Crohn's disease; CPT, current procedural terminology; DB, database; DMARD, disease-modifying antirheumatic drug; DMBA, Deseret Mutual Benefits Administration; EDC, estimated date of conception; EMR, electronic medical records; GHS, Geisinger health system; HCPCS, Health Care Financing Administration Common Procedure Coding System; HZ, herpes zoster; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; JRA, juvenile-onset rheumatoid arthritis; KPNC, Kaiser Permanente Northern California; MEDECHO, Maintenance et Exploitation des Donnees pour l'Etude de la Clientele Hospitaliere; MTX, methotrexate; NDC, National Drug Code; NJ, New Jersey; NMSC, non-melanoma skin cancer; NPV, negative predictive value; NSAID, non-steroidal anti-inflammatory drug; OSHPD, Office of Statewide Health Planning and Development; PA, Pennsylvania; PACE, Pennsylvania Assistance Contract for the Elderly; PPV, positive predictive value; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RAMQ, Regie de l'assurance maladie du Quebec; RF, rheumatoid factor; ROC, receiver operating characteristic (curve area); RX, prescription; SLE, systemic lupus erythematosus; THR, total hip replacement; VA, Veterans Affairs/Administration; VAMC, Veterans Affairs Medical Center; VISN, Veterans Integrated Services Network.

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1. Introduction

Mini-Sentinel, a pilot project sponsored by the United States Food and Drug Administration (FDA), aims to inform and facilitate the development of an active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products [1]. Mini-Sentinel is one facet of the Sentinel Initiative, an FDA effort to develop a national electronic system that will complement existing methods of safety surveillance.

To support this goal, Mini-Sentinel uses administrative and claims data to examine relationships between medical product exposures and health outcomes [1,2]. This serves to refine safety signals and facilitate active surveillance of adverse events potentially related to medical products. A first step in developing the Sentinel system is to understand the validity of algorithms (i.e., combinations of billing, procedural, or diagnosis codes, or pharmacy claims) for identifying health outcomes of interest in administrative data. Mini-Sentinel program collaborators selected health outcomes of interest using an expert elicitation process through which investigators developed a list of candidate outcomes based on input from global vaccine safety experts. A panel of 5 vaccine experts then prioritized the list via an iterative process using criteria including clinical severity, public health importance, incidence, and relevance [2].

A relationship between vaccination and autoimmune diseases such as Guillain Barré, multiple sclerosis, and type 1 diabetes has been suggested primarily based on series of individual case safety reports [3]. In rheumatology, a case series of patients developing rheumatoid arthritis (RA) after hepatitis B vaccination [4], suggested that vaccines may precipitate rheumatic autoimmune diseases, although controversy remains since previous studies failed to confirm that association [5,6] and did not find evidence for other vaccines including tetanus and influenza [7].

RA is a common disease that affects 1% of the population [8]. Patients with RA die prematurely and are at increased risk of multiple comorbidities, including infections [9]. The last two decades have brought significant changes in the management of patients with RA. These are summarized in early treatment and tight control of inflammation with the use of traditional disease-modifying antirheumatic drugs (DMARDs) and/or new biologic agents. The goal is to achieve low disease activity or remission.

Current guidelines from the American College of Rheumatology (ACR) review the use of traditional DMARDs, biologic agents, monitoring for side effects, tuberculosis screening, and the need for vaccinations in patients starting or receiving DMARDs or biologic agents [10]. However, optimal clinical use of these drugs requires accurate determination of the risks associated with their use. In rheumatology, many studies are focused on the safety of traditional and biologic DMARDs. To facilitate these studies, investigators have developed algorithms to identify patients with RA. These strategies include using multiple diagnosis codes or sets of codes and medications to define the presence of a disease.

The goal of this project was to identify algorithms used to detect RA using administrative data sources and to describe the performance characteristics of these algorithms as reported by the studies in which they were used.

2. Materials and methods

A detailed description of the methods for the project can be found in the accompanying paper by McPheeters et al. [11]. Briefly, we searched the MEDLINE database via the PubMed interface using the strategies outlined in Appendix A. We also checked the reference lists of included studies for additional relevant citations. The search strategy was developed by building on prior Mini-Sentinel approaches to searching [12]. We expanded those approaches and tested the need to incorporate additional methods, including searches of Google Scholar. This last approach did not yield any relevant citations beyond the traditional MEDLINE search.

We limited searches to the last 21 years (1991 to September 2012) and required that included studies at the abstract review stage evaluate rheumatoid arthritis and use an administrative database reporting data from the United States or Canada. The first step required that two reviewers independently determine that an abstract did not meet criteria in order to exclude the study from further review.

Second, two investigators independently assessed the full text of those studies fulfilling the abstract review criteria, with disagreements resolved via a third investigator or discussion to reach consensus. We required that studies meet the abstract review criteria and also clearly define an algorithm to identify cases of RA. We tracked whether studies reported validation of the algorithm (e.g., via chart review or independent diagnosis).

One investigator extracted data regarding the study population, outcome studied, algorithms used, validation procedure, and validity statistics. A second investigator independently verified the accuracy of the data extracted. The first author independently extracted methodologic data including elements such as the population sampled and sampling methods, methods for locating cases, and methods for validating the accuracy of diagnoses in cases located to inform the writing of the report. We summarized results of studies qualitatively and report key characteristics below.

3. Results

We identified 1218 non-duplicate citations with potential relevance; of these, 580 required full-text review. Of these, 99 studies met our inclusion criteria, and of these, nine reported methods for confirming cases identified and reported the number of cases confirmed (Fig. 1). These studies are the focus of this report (Table 1). Table 2 provides definitions for each code used in these nine studies. The other studies meeting overall inclusion criteria provided algorithms but no discussion of confirmation or validation methods and are therefore summarized in Table 3. The studies describing case confirmation were conducted using a range of data sources, including the Veterans Affairs (VA) system, tertiary care hospitals, Medicare data, and insurance company databases.

Ng et al. assessed the validity of an algorithm for identifying RA cases using VA data from one hospital in Houston, Texas [13]. The investigators then confirmed potential cases using chart review of a random sample of records stratified by several criteria. To establish the initial dataset of potential cases, the investigators sought patients with at least two ICD-9 codes of 714 (no extensions

Table 1
Characteristics of studies with validated RA algorithms ($n = 9$).

Author, Year, Country, Time Period	Data source/Population, Population N	Sample/Case characteristics[a]	Clinical event	Algorithm	Validation/Adjudication procedure, Operational definition	Validation statistics % (95% CI)
Ng et al., 2012 [13]	Houston, TX VA databases	1779 potential cases identified, mean age = 62 years, 91% male	Prevalent RA	At least 2 ICD-9 codes of 714 separated by at least 6 months	Medical record review of random sample of potential cases ($n = 543/1779$)	Study reports PPV of 30.9% for cases confirmed in the sample of 543 records; actual # of cases not reported but can be estimated at 167
United States					2 ICD codes as noted plus documentation of at least four 1987 ACR criteria or positive anti-CCP testing or patient self-report of RA management by non-VA rheumatologist	Among these 543 potential cases, PPVs (95% CI) reported by strata:
January 1998-September 2009						DMARDs ≥180 days = 60.4% (55.3%–65.5%) DMARDs≥180 days + ≥1 rheumatology clinic visit + RA code made at rheumatology clinic visit = 75.0% (67.2%–82.8%) DMARDs≥180 days + ≥1 rheumatology clinic visit + RA code at last rheumatology clinic visit = 91.4% (85.4%–97.4%) DMARDs≥180 days + ≥1 rheumatology clinic visit + RA code not made at last rheumatology clinic visit = 36.7% (22%–54.5%) DMARDs≥180 days + no RA code at rheumatology clinic visit = 4% (1.1%–13%) DMARDs≤180 days = 6.7% (4.4%–10%) DMARDs≤180 days + ≥1 rheumatology clinic visit = 2.5% (1.1%–5.8%) DMARDs≤180 days + ≥1 rheumatology clinic visit + RA code made at one rheumatology clinic visit = 5.1% (2.2%–11.3%) DMARDs≤180 days + ≥1 rheumatology clinic visit + RA code made at last rheumatology clinic visit = 7.1% (2.0%–22.7%) DMARDs≤180 days + ≥1 rheumatology clinic visit + RA code not made at last rheumatology clinic visit = 4.2% (1.5%–11.7%) DMARDs≤180 days + ≥1 rheumatology clinic visit + RA code never made at rheumatology clinic visit = 0 ($n = 99$)

Table 1 (*Continued*)

Author, Year, Country, Time Period	Data source/Population, Population N	Sample/Case characteristics[a]	Clinical event	Algorithm	Validation/Adjudication procedure, Operational definition	Validation statistics % (95% CI)
Singh et al., 2004 [14]	Minneapolis VA rheumatology clinic (hospital & pharmacy databases)	184 patients with >1 clinic visit sampled, mean age 64.4 years, 94% male; of these, 86 met gold standard criteria for RA (see Operational Definition), mean age = 65.5 years, 95% male	Prevalent cases	A1:ICD code 714 alone	Random sample of 252/737 patients seen at VA rheumatology clinic; of these, 68 records were unavailable or patient had only 1 clinic visit, thus 184 charts reviewed (among these, 86 individuals confirmed as having RA using gold standard criteria below)	A1:
United States	737			A2: ICD code 714 + 3 month	Chart diagnosis of RA by a rheumatologist on ≥2 visits >6 weeks apart	sensitivity:100% (96%–100%) specificity:55.1% (48%–62%)
January 2001 – July 2002				prescription of a DMARD (date of receipt of prescription not specified)		PPV: 66.2%(59%–73%)
				A3: ICD code 714 + a positive RF titer		NPV: 100% (NA) ROC: 77% (69%–85%)
				A4: 3 month prescription of a DMARD + positive RF		A2:
				A5: ICD-9 code 714 + DMARD + positive RF		sensitivity: 84.9% (80%–90%) specificity: 82.7% (77%–88%)
						PPV: 81.1% (75%–87%) NPV: 86.2% (81%–91%) ROC: 84% (77%–90%) A3: sensitivity: 88.2% (83%–93%) specificity: 91.4% (87%–96%) PPV: 92.6% (88%–97%) NPV: 86.5% (81%–92%) ROC: 90% (84%–95%) A4: sensitivity: 76.5% (70%–83%) specificity: 95.7% (92%–99%) PPV: 95.6% (92%–99%) NPV: 77% (70%–84%) ROC: 86% (80%–92%) A5: sensitivity: 76.5% (70%–83%) specificity: 97.1% (94%–100%) PPV: 97% (94%–100%) NPV: 77.3% (71%–84%) ROC: 87% (81%–93%)

Katz et al., 1997 [16]	8 rheumatology offices in MA, CO, & VA (Medicare Physician claims (Part-B) database)	153 subjects with RA documented in medical record (defined as presence of one of the codes in algorithm column)	Prevalent cases	ICD-9: 714.0, 714.1, 714.2, 714.3,714.30, 714.31, 14.32,714.33	Medical record review	Sensitivity: 90% (85%–95%)
						PPV: 95% (92%–98%)
United States	3373			CPT codes indicating joint and soft tissue injection and aspiration (20550, 20600, 20605)	Diagnosis identified in the medical record was coded on the same day (± 2 days) in the physician claims data	
Liao et al.,2010 [17]	Partners HealthCare EMR (narrative & codified data)	500 individuals with RA from 2 large hospitals (Brigham & Women's and Mass General) with ≥1 ICD-9 code for RA & related diseases or who had anti-CCP	Prevalent cases	ICD-9 = 714.x	Blinded medical record review by 2 rheumatologists on 500 random patients from the subset of patients classified as RA by any of the 3 algorithms	A1: PPV:94% (91%–96%)
United States						sensitivity: 63% (51%–75%)
	29,432 subjects	Age: 60.4 ±1.6 (n = 96)		A1: Narrative & codified data	Rheumatologists diagnosed RA & fulfilling 1987 ACR criteria	
October 1994–June 2008						A2: PPV: 88% (84%–92%)
				A2: Codified data only[b]		sensitivity: 51 (42%–60%)
				A3: Narrative data only		A3: PPV:89% (86%–93%)
				A4: ≥3 ICD-9 RA codes ≥7 days apart		sensitivity: 56% (46%–66%) A4: PPV:56% (47%–64%)
				A5: ≥1 ICD-9 RA code separated by > 7 days, plus > = 1 DMARD		sensitivity: 80% (72%–88%)
						A5: PPV:45% (37%–53%) Sensitivity: 66% (57%–76%) PPV
Kim et al., 2011 [18]	Medicare (claims data) beneficiaries in PA Assistance Contract for the Elderly (PACE) program	158 study subjects who were 65 years or older	Prevalent cases	A1: beneficiaries with at least 2 claims associated	Medical record review by rheumatologist	
United States				with RA (ICD-9-CM: 714 without extensions)		
	9482				Gold standard definition:	No DMARD RX needed: RA as per rheumatologists:
1994–2004 (claims data)				A2: beneficiaries with at least 3 claims associated with RA		
					1) diagnosis of RA by a rheumatologist and	A1: 55.7% (46.8%–64.4%)

Table 1 (*Continued*)

Author, Year, Country, Time Period	Data source/Population, Population N	Sample/Case characteristics[a]	Clinical event	Algorithm	Validation/Adjudication procedure, Operational definition	Validation statistics % (95% CI)
2004–2008 (medical records)				A3: beneficiaries with at least 2 RA claims from a rheumatologist and were separated by at least 7 days	2) fulfillment of the 1987 ACR criteria for RA	A2: 65.5% (55.8%–74.3%) A3: 66.7% (55.5%–76.6%) ≥4 ACR criteria: A1: 33.6% (25.6%–42.4%) A2: 40% (30.8%–49.8%) A3: 39.3% (28.8%–50.6%) ≥3 ACR criteria: A1: 42.8% (34.2%–51.7%) A2: 50.9% (41.2%–60.6%) A3: 50% (38.9%–61.1%) Requires 1 DMARD RX: RA as per Rheumatologists: A1: 86.2% (74.6%–93.9%) A2: 87.5% (75.9%–94.8%) A3: 88.9% (76%–96.3%) ≥4 ACR criteria: A1: 58.6% (44.9%–71.4%) A2: 60.7% (46.8%–73.5%) A3: 55.6% (40%–70.4%) ≥3 ACR criteria: A1: 72.4% (59.1%–83.3%) A2: 75% (61.6%–85.6%) A3: 73.3% (58.1%–85.4%)
Losina et al., 2003 [19] United States 1995	Inpatient Medicare claims data for patients who received elective primary total hip replacement (THR) & THR recipients from Ohio, Pennsylvania and Colorado NR	922 patients with RA	Prevalent cases	ICD-9-CM 714 without extensions or 714.0 recorded in both hospital and surgeon's Medicare claims	Medical record review for a single hospitalization	Sensitivity: 65% (49%–80%) PPV: 86% (73%–99%)
Klein et al., 2009 [20]	HMO DB (Kaiser Permanente, Northern California—KPNC)	Disease free inception cohort of KPNC members for at least 77/84 months during the study period and members for at least 22 of 24 months from Jan 1996–Dec 1997 Age: 10–62 years	Incident cases[b]	ICD-9 code and text write-in diagnosis	All 48 electronic records of JRA and a random sample 100 cases of RA medical charts	Proportion verified after medical record review: JRA: 47.1% (34%–62%)

United States January 1998-December 2004	3.2 million			ICD-9: Juvenile RA: 714.30, 714.31, 714.32, 714.33 RA: 714.0, 714.1, 714.2, 714.81, v82.1	Two clearly stated diagnoses of JRA or Still's disease or RA, with at least one diagnosis by a rheumatologist	RA: 48% (38%–58%)
Bili et al., 2011 [21]	All adults ≥18 years of age with a diagnosis of RA within the Geisinger Health system, a primary care and multispecialty medical practice in PA	1127 incident cases of RA	Incident cases[b]	Primary or secondary diagnosis with ICD-9 code of 714.0 at ≥2 outpatient encounters with a Geisinger Health System rheumatologist.	Manual review of 100 random charts and diagnosis validated against 1988 ACR criteria	PPV: 97% (92%–99%)
United States January 2003-March 2008	2093					
MacLean et al., 2001 [22]	Unspecified large West coast insurance company database	2244 individuals with RA identified by algorithm	Prevalent cases	≥65 years, ≥2 physician visits (CPT codes 99201–99205 and 99211–99215) with a diagnosis code for RA (ICD–9 codes 714.0, 714.1, 714.2, 714.81) with at least 30 days between any 2 of the visits	Mailed survey to individuals identified via algorithm–brief self-report questionnaire assessing whether individual had ever been diagnosed with arthritis and type if so; response options included RA	PPV: 92% (91%–94%; Self-report among 924/2244 individuals responding to survey; among 893/924 returned surveys with complete responses, 825 individuals self-reported physician diagnosis of RA)
United States September 1997–August 2000	1.4 million continuously enrolled beneficiaries					

[a] Data reported in this column are either the # of confirmed cases (where reported) or the number of cases identified, but not necessarily confirmed, using the search algorithm. **Codified data = ICD-9 RA, normalized ICD-9 RA, anti-TNF, RF positive, and methotrexate for positive predictors, and ICD-9 JRA, ICD-9 SLE, and ICD-9 PsA for negative predictors.

[b] Diagnosis-free baseline period was 2 years.

Table 2
RA diagnostic and procedural codes used in studies describing case validation methods.

Study	Algorithm	Definition
Ng et al., 2012 [13]	714	Rheumatoid arthritis and other inflammatory polyarthropathies
Singh et al., 2004 [14]	714	Rheumatoid arthritis and other inflammatory polyarthropathies
Katz et al., 1997 [16]	714.0	Rheumatoid arthritis
	714.1	Felty's syndrome
	714.2	Other rheumatoid arthritis with visceral or systemic involvement
	714.3	Juvenile polyarthritis
	714.30	Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
	714.31	Polyarticular juvenile rheumatoid arthritis, acute
	714.32	Pauciarticular juvenile rheumatoid arthritis
	714.33	Monoarticular juvenile rheumatoid arthritis
	CPT Codes	
	20550	Injection, tendon sheath, ligament, trigger points or ganglion
	20600	Arthrocentesis, aspiration, and/or injection; small joint, bursa or ganglion
	20605	Arthrocentesis, aspiration, and/or injection; intermediate joint, bursa or ganglion
Liao et al.,2010 [17]	714.x	Rheumatoid arthritis and other inflammatory polyarthropathies
Kim et al., 2011 [18]	714	Rheumatoid arthritis and other inflammatory polyarthropathies
Losina et al., 2003 [19]	714	Rheumatoid arthritis and other inflammatory polyarthropathies
	714.0	Rheumatoid arthritis
Klein et al., 2009 [20]	714.30	Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
	714.31	Polyarticular juvenile rheumatoid arthritis, acute
	714.32	Pauciarticular juvenile rheumatoid arthritis
	714.33	Monoarticular juvenile rheumatoid arthritis
	714.0	Rheumatoid arthritis
	714.1	Felty's syndrome
	714.2	Other rheumatoid arthritis with visceral or systemic involvement
	714.81	Rheumatoid lung
	v82.1	Rheumatoid arthritis
Bili et al., 2011 [21]	714.0	Rheumatoid arthritis
MacLean et al., 2001 [22]	714.0	Rheumatoid arthritis
	714.1	Felty's syndrome
	714.2	Other rheumatoid arthritis with visceral or systemic involvement
	714.81	Rheumatoid lung
	CPT Codes	
	99201	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: a problem focused history; a problem focused examination; straightforward medical decision making.
	99202	Ffice or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: an expanded problem focused history; an expanded problem focused examination; straightforward medical decision making
	99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: a detailed history; a detailed examination; medical decision making of low complexity
	99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of moderate complexity.
	99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of high complexity
	99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services
	99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: a problem focused history; a problem focused examination; straightforward medical decision making
	99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: an expanded problem focused history; an expanded problem focused examination; medical decision making of low complexity
	99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: a detailed history; a detailed examination; medical decision making of moderate complexity
	99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of high complexity

specified) separated by at least six months and treated between 1998 and 2009. This initial search located 1779 potential cases. The investigators sought to validate a sample of cases ($n = 543$) via chart review by two physicians. They considered true cases as those with at least two diagnosis codes as noted plus documentation of at least four 1987 ACR classification criteria or positive testing for antibodies to cyclic citrullinated peptide (anti-CCP) or when the patient reported RA management by a non-VA rheumatologist. The sample of charts for review was stratified into groups on the basis of DMARDs use, rheumatology clinic visits, assignment of RA codes at any or the last rheumatology visit, and PPV assessed for each stratum.

Among the 543 cases selected for chart review, approximately 167 were confirmed as cases for a PPV of 30.9%. Positive predictive values for each of the individual strata are reported in the table; the highest PPV was found in those cases that had been on DMARDs for at least 6 months, had made at least one visit to a rheumatologist, and had an RA code made at their latest visit to the rheumatology clinic (91.4%). Use of DMARDs and an RA code made at a rheumatology clinic but not at the latest rheumatology visit had a PPV of 36.7%. No algorithm among the subpopulation that had been on DMARDs for less than 180 days had a PPV greater than 15% [13].

Singh et al. used data from the Minneapolis VA hospital to validate diagnoses of RA, with a focus on assessing the adequacy of

Table 3
Publications providing algorithm without discussion of verification methods ($n = 90$)[b].

Author, Year, Country Time Period	Data source	Algorithm
Beukelman et al., 2012 [29]	US Medicaid Analytic eXtract	At least 2 ICD-9 codes 714 (no extension given), 696.0, 720, 713.1 + 555, or 713.1 + 556 from physician evaluation at least 7 days but no more than 183 days apart + age <16 years or a single code + outpatient pharmacy claim for TNF inhibitor, methotrexate, or leflunomide with 183 days + age <16 years
2000–2005		
Blumenthals et al., 2012 [30]	MarketScan	At least 2 claims coded with ICD-9 codes 714.0 or 714.2 + age ≥18 years
1/2000–12/2007		
Chu et al., 2012 [31]	California Medicaid database	At least 1 diagnosis of RA (ICD-9 714.0–714.18) + 1 DMARD prescription (methotrexate, hydroxychloroquine, leflunomide and sulfasalazine, adalimumab, anakinra, etanercept, and infliximab) + age >18 years
1/1998–12/2005		
De Vera et al., 2012[a] [32]	British Columbia Ministry of Health database	At least 2 physician visits at least 2 months apart with ICD-9 code 714; cases were excluded if at least 2 visits subsequent to second RA visit had diagnosis of other inflammatory arthritides or if RA visit coded by a non-rheumatologist was not confirmed by subsequent rheumatologist visit or if there were no subsequent RA-coded visits during at least 5 years of follow-up
5/1996–3/2006		
Jain et al., 2012 [33]	Nationwide Inpatient Sample	ICD-9-CM 714.0
1992–2005		
Kim et al., 2012 [34]	Blue Cross/Blue Shield database	At least 2 visits coded with ICD-9-CM 714.xx + 1 filled DMARD prescription
1/2005–6/2008		
Kim et al., 2012 [35]	Canadian Provincial health care system database, US commercial insurance plan database	At least 2 inpatient or outpatient visits coded with ICD-9-CM 714.xx separated by 12 months of continuous health plan coverage + 1 filled DMARD prescription + age >18 years
1/1996–6/2008		
Rogers et al., 2012 [36]	Medicare database, Health and Retirement Study database	ICD-9 714.0–714.8
1991–2007		
Widdifield et al., 2012 [37]	Ontario Health Insurance Plan database, Canadian Institute for Health Information Discharge Abstract Database, National Ambulatory Care Reporting System, Ontario Drug Benefit Program database	At least 2 codes of ICD 714 more than 60 days apart but within 5 years + at least 1 prescription for DMARD, glucocorticosteroid, or biologic + age ≥66 years
4/1992–3/2010		
Amari et al., 2011 [38]	Austin Information Technology Center and the pharmacy benefits management databases	ICD-9-CM diagnosis code 714.0, 714.1, 714.2 or 714.81 + ≥ 1 DMARD prescription from the VA + ≥ 4 month history of receiving medication from the VA before the first DMARD prescription + ≥ 2 separate clinic visits during the study period excluding patients with a diagnosis of NMSC at any time before receiving their first DMARD + age or gender recorded + race recorded
US		
10/1998–9/2008		
Bili et al., 2011 [39]	Geisinger Health System (GHS) Electronic Health Records	ICD-9 code 714.0 in ≥ 2 office visits with a GHS rheumatologist at any time during study period
US		
9/2000–3/2008		
Curtis et al., 2011 [40]	Premier Perspective database	≥1 inpatient medical service claims coded with ICD-9-CM 714.xx
US		
1/2004–9/2009		
Curtis et al., 2011 [41]	Aetna administrative medical and pharmacy databases	Age < 65 yrs unless enrolled in Medicare Advantage plan (and not commercially insured) + no history of hospitalization for GI perforation or inflammatory bowel disease during baseline period + ICD-9-CM code 714.x with prescription for, or infusion of anti-TNF or MTX OR 2 ICD-9-CM code 714.x diagnoses separated by >7 days but within 6 months of each other + insurance coverage in 6 months prior to index date and throughout followup
US		
1/2005–8/2009		

Table 3 (*Continued*)

Author, Year, Country Time Period	Data source	Algorithm
Curtis et al., 2011 [42] US 1/2005–8/2009	Aetna's administrative medical and pharmacy databases	Age < 65 years unless enrolled in Medicare Advantage plan (with pharmacy benefit) + ICD-9-CM code 714.x with prescription for MTX or biological agent OR 2 ICD-9-CM code 714.x diagnoses separated by >7 days but within 1 year + ≥ 1 prescription or infusion for anti-TNF or non-anti-TNF biological agent, not received within prior 12 months + medical and pharmacy benefits in 12 months before index date and throughout followup, excluding patients with malignancy (excluding non-melanoma skin cancer)
DeVera et al., 2011 [43,44] Canada 5/1996–3/2006	British Columbia Ministry of Health database	Age ≥ 18 yrs + at least 2 physician visits ≥2 months apart with an RA diagnosis code (ICD-9 714.x) + subsequent RA-coded visits in at least 5 years of follow-up + no more than 1 diagnosis of other arthritides after second visit + no visits coded as RA by non-rheumatologist not confirmed on subsequent rheumatologist visit
Dixon et al., 2011 [45] Canada 1/1985–12/2003	Regie de l'assurance maladie du Quebec (RAMQ); Ministry of Health's Maintenance et Exploitation des Donnees pour l'Etude de la Clientele Hospitaliere (MEDECHO)	Age >65 yrs + ≥ 1 traditional or biological DMARD in RAMQ prescription program + coded with ICD-9 714.x + ≥ 3 months health plan eligibility prior to cohort entry
Farng et al., 2011 [46] US 1995–2005	California Office of Statewide Health Planning and Development (OSHPD) patient discharge database	Patients undergoing primary total or hemiarthroplasty of the shoulder during study period + concurrent diagnosis of proximal humeral fracture or appropriate non-fracture diagnosis (osteoarthritis, rheumatoid arthritis—ICD-9 714.0, 714.2, 714.30, 714.31, 714.32, 714.33—other inflammatory arthropathy, or avascular necrosis of the humeral head), excluding patients with other trauma of the upper extremity, prior shoulder dislocation, malignancy, prior infection of the shoulder, prior surgery such as hardware removal, arthrodesis, or internal fixation, or with ZIP codes outside of California
Kuriya et al., 2011 [47] US 1/2002–6/2008	HealthCore Integrated Research Database	Ages 18–45 years on ECD + 2 visits coded with ICD-9 714.x + ≥ 12 months health plan eligibility prior to start of follow-up + ICD-9 codes 72.0–75.9, 630–639.9, 640–648.9, 650–669.99, 670–676.9, V22–V22.2, V23–V23.9, V24.0–V24.2, V27–V27.9, V30–V39.2 or CPT codes 01960–01969, 58605, 58610–58611, 59160, 59300,59305, 59400, 59409–59414, 59425–59426, 59430, 59510,59514–59515, 59525, 59612, 59614, 59620, 59622, 59812,59820–59821, 59830, 59840–59841, 5985, 59857, 59870,59899, 99436 OR ICD-9 codes 75.0, 630, 632, 634–639.9 or CPT codes 01960–01969, 59812, 59820–59821, 59830,59840–59841, 59850–59857, 59870 + health plan coverage for at least 180 days prior to EDC and throughout the pregnancy + ≥ 180 days between any 2 EDCs for one woman
Lane et al., 2011 [48] US 10/1998–9/2005	US Veteran's Affairs national databases including Pharmacy Benefits Management database	At least 1 inpatient or outpatient ICD-9CM code of 714.0 or 714.1 or 714.2 or 714.81 + subsequent receipt of one of the following: hydroxychloroquine, auranofin, injectable gold, penicillamine, sulfasalazine, methotrexate, azathioprine, leflunomide, cyclophosphamide, anakinra, etanercept, infliximab, adalimumab + receipt of any medication for at least 4 months prior to first DMARD prescription + at least 2 separate outpatient or inpatient clinical encounters during study period + age and sex recorded
Louder et al., 2011 [49]	Humana Medicare database	At least 1 medical claim with 714.x or v82.1 or 715.x in any of first 3 diagnosis fields between 1/2007–12/2007 and Medicare Advantage or Medicare Supplemental coverage for 365 days prior to and after index date excluding patients with an ICD-9-CM code 211.3 or 720.0

US 1/2006–12/2008 McBride et al., 2011 [50]	Unspecified US large administrative claims database	Age 18–65 and at least 2 diagnoses (primary or secondary) with ICD-9 code 714.xx recorded in medical service claims and at least 1 claim for a TNF-α antagonist therapy identified using J-codes on medical claims (provider-administered drugs) and NDC codes on pharmacy claims (self-administered drugs) + continuous health plan enrollment and 6 months eligibility prior to initiation of TNF-α and 24 months continuous eligibility post-initiation. Subjects were excluded if they had a diagnosis of psoriasis (696.xx) or Crohn's disease (555.xx) or incomplete prescription drug records.
US 1999–2007 Solomon et al., 2011 [51]	British Columbia provincial health care system, a commercial US health plan (unnamed)	Age ≥ 18 yrs + ICD-9 code 714.x, 696.0, or 696.1 diagnosis at ≥ 2 physician visits, ≥ 7 days apart + continuous enrollment in health plan for 12 months prior to second diagnosis + ≥ 1 filled prescription for a DMARD before start of follow-up, excluding patients with ICD-9 code 250.x in 12 months before second diagnosis
US/Canada 1/1996–6/2008 Winthrop et al., 2011 [52]	Kaiser Permanente Northern California, Portland Veterans Affairs Medical Center	At least one clinical visit and ≥1 outpatient prescription for etanercept or adalimumab, or at least one infusion of infliximab + ICD-9 code 714
US 1/2000–12/2008 Bartels et al., 2010 [53]	US Veteran's Health Administration database	ICD-9 codes representing the top 10–13 corresponding diagnoses per encounter for RA (714.0); Felty syndrome (714.1); RA lung disease including interstitial lung disease and pleurisy (714.8, 515.0, 517.8, 511.0 or 511.9, combined with a simultaneous 714.0 code indicating RA); carditis (714.2); or vasculitis
US 1985–2006 Ferucci et al., 2010 [54]	Alaska Native Medical Center database	ICD-9 code 714.0 + documentation of the diagnosis of RA fulfilling the 1987ACR classification criteria
US 10/2000–9/2005 Kim et al., 2010 [55]	HealthCore Integrated Research database	Age ≥18 years + at least 2 visits for RA coded with ICD 9-CM 714.xx
US 1/2001–7/2008 Petri et al., 2010 [56]	Thomson's MarketScan Commercial Claims and	At least 2 claims for RA (ICD 9: 714.0[a], 714.1[a], 714.2[a], and 714.3[a]) that were non-diagnostic (i.e. not blood, lab, radiological claims) with active insurance status on June 30, 2007 and at least 1 diagnosis of RA before July 1, 2006
US 1/1999–6/2007 Solomon et al., 2010 [57]	Encounters Research Database, Medicare Supplemental Medicare (PA/NJ)	Recorded diagnoses for osteoarthritis or rheumatoid arthritis on 2 separate visits + filled analgesic prescription after second visit, excluding patients who used drugs in 180 days before index date, patients with diagnosis of malignant neoplasm, use of hospice services in past 365 days, or dispensing of analgesics from 2 categories simultaneously. Consistent use of health care system services in preceding 365 days was required.
US 1/1999–12/2005 Solomon et al., 2010 [58]	British Columbia Medical Services Plan database	At least 2 visits for RA (ICD-9-CM 714.0) at least 1 week apart, excluding those with diabetes (250.xx) (RA cohort)
Canada 1/1996–12/2006 Bartels et al., 2009 [59]	US Veterans Health Administration system database	ICD-9 code 714.0 + ≥1 of codes 447.6, 354.1, 354.2, 354.3, 354.8,354.9, 355, 357.1, 785.4, 707.1 and not having ICD-9 code 250
US 1985–2006 (hospitalized patients) or 1997–2006 (ambulatory patients)		

Table 3 (*Continued*)

Author, Year, Country Time Period	Data source	Algorithm
Brassard et al., 2009 [60] Canada 1/1980–12/2003	Provincial administrative databases for Quebec	Age ≥ 65 years + receive social assistance + no private drug insurance + ≥ 1 diagnosis of RA (ICD-9 code 714) + ≥ 1 prescription for DMARD therapy
Cook et al., 2009 [61] US 1988–2005	Nationwide Inpatient Sample	ICD-9 code 714.0 or 714.1 or 714.2 + code 81.84 (total elbow replacement)
Gadalla et al., 2009 [62] US 1993–2002	SEER–Medicare data linkage datasets	At least one inpatient or two outpatient/physician claims (with a minimum interval of 30 days between claims) + any of the following RA ICD-9 codes: 714.0, 714.1, 714.2, 714.3, 714.81, or V82.1 + incident primary invasive adenocarcinoma of the breast
Liang et al., 2009 [63] US 1/1990–1/2000 (ANA testing) and/or 9/2003–1/2005 (CCP testing) until 4/2007	Rochester Epidemiology Project database	RF and/or ANA testing and/or CCP + ICD-9 714.0–714.2, 714.81
Matta et al., 2009 [64] US 1979–2005	National Hospital Discharge Survey	ICD-9-CM 714.0
McDonald et al., 2009 [65] US 10/1998–6/2005	Austin Automation Center database	Veterans with ICD-9-CM code diagnosis of RA (714.0, 714.1, 714.2, 714.81) + ≥ 4 month history of receiving medications from the VA during the study period + subsequently received a first prescription for a DMARD, excluding patients with diagnosis of HZ prior to DMARD or without ≥ 2 separate clinical encounters during study period
Molloy et al., 2009 [66] US 1998–2005	US Nationwide Inpatient Sample (NIS) database	ICD-9 codes 714.0, 714.0–714.9, 710.0, 710.1, 710.2, 710.3, 710.4, 710.0–710.9, 720.0, 696.0, 711.1, 711.3, 099.3, 720.89, 720.9, 446.0, 446.1, 446.20, 446.29, 446.4, 446.5, 446.7, 437.4, 447.6
Pariikh-Patel et al., 2009 [67] US 1991–2002	California Office of Statewide Planning and Health Development	ICD-9 codes 714.0–714.2 designated in any of the 25 diagnostic fields (principal diagnosis and up to 24 other diagnoses)
Patkar et al., 2009 [68] US 1/2002–12/2003	University of Alabama at Birmingham (UAB) health system claims database	Age ≥ 18 yrs + ≥1 ICD-9 codes 714.x at any position on billing claim
Scherrer et al., 2009 [69] US 1999–2006 (fiscal year)	US Veterans Administration Corporate Data Warehouse + Pharmacy Benefits Management databases	ICD-9 codes 714.0, 714.1, 714.2, or 714.81 + use of ≥ 1 DMARD during study period
Silverman et al., 2009 [70] US 2001–2004	MarketScan databases: Commercial Claims and Encounters database, Health and Productivity Management database	Ages 18–64 + ≥ 18 months medical claims data history + concurrent prescription drug coverage and data availability + [(Cohort 1) ≥ 2 non-diagnostic claims with ICD-9 codes 729.1, ≥ 365 days apart] OR [(Cohort 2) ≥ 2 non-diagnostic claims with ICD-9 codes 714.0x, 714.1x, 714.2x, 714.3x, ≥ 30 days apart] OR [(Cohort 3) meeting both aforementioned criteria]
Barnabe et al., 2008 [71]	Manitoba Health research data repository	Age 18 and over + at least 1 physician claim or hospital discharge diagnosis coded with -ICD-9 714, 715, or 716

Canada 1995–2000 Bernatsky et al., 2008 [72]	Regie d'assurance maladie	ICD-9 code 714 + at least one DMARD exposure after January 1, 1980 + >3 months health insurance coverage + no cancer diagnoses
Canada 1/1980–12/2003 Cohen et al., 2008 [73]	du Quebec physician billing and pharmacy claims databases, and the provincial hospitalization database IMS Health Integrated Administrative Claims Database, MarketScan Commercial Claims and Encounters Database	At least 1 ICD-9 code of 714.x in the treatment record + code for IBD
US 1/2001–12/2002 Feldman et al., 2008 [74]	Regie de l'Assurance Maladie du Quebec	Age 16 or younger + physician visit in 2000 + ICD-9CM code 714
Canada 1/1997–6/2003 Grijalva et al., 2008 [75]	TennCare (Medicaid) database	Age ≥ 18 yrs + ICD-9 codes 714.0, 714.1, 714.2, 714.3, 714.30, 714.31, 714.32, 714.33, 714.4, or 714.81 (excluding those with an ICD-9 code for unspecified inflammatory arthropathies) + 1 hospitalization discharge diagnosis of RA OR 1 ambulatory visit resulting in diagnosis of RA and a prescription for DMARD OR 2 ambulatory visits (≥ 1 month apart) that resulted in a diagnosis of RA + ≥ 1 prescription filled during baseline. Patients with solid organ transplantation, HIV/AIDS, cancer (except non-melanoma skin cancers), and serious renal, liver, or respiratory diseases identified during the baseline period were excluded.
US 1995–2004 Grijalva et al., 2008 [76]	TennCare (Medicaid) database	Age ≥ 18 yrs + ICD-9 codes 714.0, 714.1, 714.2, 714.3, 714.30, 714.31, 714.32, 714.33, 714.4, or 714.81 + filling at least 1 DMARD prescription
US 1995–2004 Han et al., 2008 [77]	MarketScan database	Age 17 or greater + continuous enrollment in medical/drug benefit plan + ICD-9 code 714.x + treatment with any DMARD in 2004
US 1/2004–12/2004 Hochberg et al., 2008 [78]	MarketScan databases	Age 18 or greater + ICD-9-CM code 714.0x on 3 non-diagnostic claims on different days + [incident sample] 12 continuous enrollment prior to and for 24 months following first RA diagnosis
US 1/1999–9/2006 Janicke et al., 2008 [79]	Florida Medicaid database	Age 5–18 years + ICD-9 714.30 or 714.31 or 714.32 or 714.33
US 2001–2005 Khurana et al., 2008 [80]	US Veteran Administration VISN database	ICD-9 code 714.0
US 10/1998–6/2004 Lacaille[a] et al., 2008 [81]	Ministry of Health of British Columbia administrative billing database	ICD-9 code 714.x at ≥ 2 physician visits, > 2 months apart, excluding individuals with ≥ 2 visits after second visit that included diagnoses of other inflammatory arthritides and individuals without confirmation of diagnosis by rheumatologist
Canada 1/1996–3/2003 Smitten et al., 2008 [82]	PharMetrics database	Age 18 years or older + at least 2 physician visits more than 2 months apart coded with ICD-9-CM 714 excluding 714.3, 714.4, 714.9
US 1/1999–7/2006 Ting et al., 2008, 2005 [83,84]	US Veterans Administration health system database-New England region	At least 2 recorded visits with a diagnosis of RA (ICD-9-CM 714.0) + at least 2 outpatient visits from hospitals within the New England VA Health System from July 1999 to June 2001 + sufficient evidence of RA in the medical record

Table 3 (*Continued*)

Author, Year, Country Time Period	Data source	Algorithm
US 6/2000–6/2001 Bernatsky et al., 2007 [85]	Regie d'assurance maladie du	Diagnosis of RA (ICD-9 714) + at least 1 DMARD (methotrexate, hydroxychloroquine, chloroquine, sulphasalazine, azathioprine, leflunomide, cyclophosphamide, cyclosporine, gold compounds, minocycline, penicillamine and TNF-alpha antagonists) dispensed
Canada 1/1980–12/2003 Curtis et al., 2007 [86,87]	Quebec (RAMQ) and Ministry of Health's Maintenance et exploitation des donnees pour l'etude de la cliente le hospitaliere (MEDECHO) databases UnitedHealth group medical and pharmacy administrative claims database	Age 18 or older + at least 2 ICD-9-CM codes of 714.x excluding 714.3 + infusion/prescription for infliximab or adalimumab or etanercept or MTX ± TNFα antagonist or at least prescriptions for MTX
US 5/1998–12/2003 Curtis et al., 2007 [88]	UnitedHealth group medical and pharmacy administrative claims database	Age <50 years + at least two ICD-9-CM diagnosis codes for RA (714.X) + infusion or filled a prescription for a TNF-α antagonist + or filled at least three prescriptions for one of several selected immunosuppressive drugs
US 1/1998–12/2002 Curtis et al., 2007 [89]	UnitedHealth Group database	ICD-9 code 714.x or 555.x during 6 months prior to study period + ≥ 3 filled prescriptions of etanercept, infliximab, or MTX (for RA patients) OR infliximab, methotrexate, 6-mercaptopurine, azathioprine, or prednisone (for CD patients), excluding patients with any claim for HIV, organ transplant, or solid tumor malignancies
US 1/1998–12/2002 Khanna et al., 2007 [90]	West Virginia Medicaid database	>1 medical service claim for a hospitalization, emergency department visit, or office visit with a primary diagnosis of RA (ICD-9-CM code 714.00) + age 15–64 years
US 2003 Lee et al., 2007 [91]	US Veterans Health Administration	Age 55–64 + ICD-9 code 714 or 714.0
US 2000–2004 Sacks et al., 2007 [92]	National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey office visit, hospital outpatient, and emergency department visit data	Any of the following ICD-9-CM codes for JRA: 099.3, 136.1, 274, 277.3, 287.0, 390, 391, 437.4, 443.0, 446, 447.6, 695.2, 696.0, 701.0, 710, 711, 712, 713, 714, 715, 716, 719.3, 719.3, 720, 727.0, 729.0, 729.1
US 2001–2004 Smitten et al., 2007 [93]	US PharMetrics claims database	At least 18 years of age + at least one ICD-9-CM code for RA (714; excluding 714.3, 714.4, 714.9), excluding patients enrolled in Medicare gap plans, missing age or sex data, with <90 days continuous enrollment, or with a diagnosis of herpes zoster in 90 days prior to cohort entry
US 1998–2002 Weng et al., 2007 [94]	Kaiser Permanente Northern California	2 or more inpatient or outpatient ICD-9-CM codes for RA (714.0 or 714.3)
US 1996–2005 Brassard et al., 2006 [95]	US PharMetrics Patient-Centric Database	≥ 1 ICD-9 code 714 during inpatient or outpatient visit + at least 1 prescription for any anti-RA drug including DMARDs
Canada 9/1998–12/2003 Canales et al., 2006 [96]	Administrative database of the rheumatology clinics at the Veterans Affairs Medical Center (VAMC) and the University of Minnesota	ICD codes 720.0, 696.0, 714.0, or 711.11–711.19/099.3 + seropositivity for rheumatoid factor
US NR Han et al., 2006 [97]	US PharMetrics Patient-Centric Database	At least 1 ICD-9 code for RA (714.x) + continuous health plan enrollment in study period

US 1/2001–12/2002 Reed et al., 2006 [98]	Birth Events Records Database (Comprehensive Hospital Abstract	Female with diagnosis of RA (ICD-9 714.0) in any one of 9 diagnosis fields and during birth hospitalization or previous hospitalization
US 1987–2001 Robinson et al., 2006 [99]	Reporting System [CHARS] + birth certificate data) 2 unspecified US administrative databases, one containing data from self-insured individuals and some Medicare populations with medical and drug benefit coverage + a database including health plan data with some Medicaid, Medicare, and pension- plan patients with drug and medical coverage; both datasets drew primarily from the Midwestern and Southern US	At least 1 inpatient or at least 2 ambulatory visits coded with ICD-9 714.x
US 1/2001–12/2002 Seeger et al., 2006 [100]	Ingenix Research Database (sourced from UnitedHealthcare)	At least 1 diagnosis and surgical or nonsurgical code for Achilles tendon rupture (ICD-9 code or CPT codes 27605, 27606, 27650, 27652, 27654, 01472) + ICD-9 code 714.x + minimum 180 days plan enrollment prior to case date
US 1/1997–6/2001 Solomon et al., 2006 [101]	Medical records database of US rheumatology practice	ICD-9 code 714.xx + documentation of diagnosis of RA in medical record + at least 2 visits for RA in 2004
US 2004 Solomon et al., 2006 [102]	British Columbia Medical Services Plan database	Age ≥18 years + 3 diagnoses (ICD-9-CM 714) over 2 years
Canada 1999–2003 Suissa et al., 2006 [103]	PharMetrics Patient-Centric Outcomes Database	Physician visit coded with ICD-9 714 + prescription for anti-rheumatic drugs (methotrexate, antimalarials, hydroxychloroquine and chloroquine, leflunomide, biologic agents, sulfasalazine, gold compounds, minocycline, penicillamine, and immunosuppressants) as well as glucocorticoids, NSAIDs, and COX-2 inhibitors)
North America 1/1999–12/2003 Suissa et al., 2006 [104]	PharMetrics Patient-Centric Database	At least 1 diagnosis coded with ICD-9 714 + at least 1 DMARD prescription (leflunomide, methotrexate, all biologic agents, gold compounds, antimalarial drugs, minocycline, penicillamine, sulfasalazine, and cytotoxic agents) after 9/1998
North America 1/1995–12/2003 Weir et al., 2006 [105]	Deseret Mutual Benefits Administration (DMBA) database	ICD-9-CM code 729.1, except for the year 1997 to limit to incident cases, + 714.0
US 1997–2002 Bernatsky et al., 2005 [106,107]	Protocare longitudinal health benefit claims database	Age at least 18 years + Diagnosis of RA coded with ICD-9 714 + at least one DMARD (methotrexate, hydroxychloroquine, chloroquine, leflunomide, TNF-α antagonists, sulphasalazine, ciclosporin, gold compounds, minocycline, penicillamine, azathioprine and cyclophosphamide) after 1 September 1998 + >3 months health plan enrollment + no history of congestive heart failure
US 1/1998–12/2001 Mauldin et al., 2005 [108]	and the PharMetrics Integrated Outcomes Database Oklahoma City and Billings area Indian Health Services databases	≤ 19 years of age + ICD-9 code 714.0 or 714.2 or 714.30 or 714.33
US 1998–2000 Nissenson et al., 2005 [109]	Medstat MarketScan database	ICD-9-CM code 714.0 or 714.1 or 714.2 or 714.81 or 714.89 + enrollment in health plan with complete capture of inpatient and outpatient data and outpatient prescriptions + anemia as identified by presence of at least 1 diagnosis code for anemia (occurring in any position on a claim), 1 CPT4 or ICD-9-CM or HCPCS procedure code, or 1 drug code indicative of anemia treatment
US 1/1998–6/2001		

Table 3 (*Continued*)

Author, Year, Country Time Period	Data source	Algorithm
Briesacher et al., 2004 [110] US 2000	MarketScan Research Database	At least 1 primary or secondary inpatient or outpatient claim coded with ICD-9 714.xx or 715.xx + NSAID prescription + evidence of prescription drug plan coverage
Ward 2004 [111] US 1983–2001	California Office of Statewide Health Planning and Development database	Age 18 or older + at least ICD-9-CM code of 714.0 + either 447.6 or 354.5 or any combination of 354.1, 354.2, 354.3, 354.8, 354.9, 355.0, 355.2, 355.3, 355.4, 355.7, 355.79, 355.8, or 355.9 or 357.1 or 785.4 in the absence of 250.7 or 707.1 (unless 707.1 also appearing with 99.25 but without 140.0–239.9) OR age 18 or older + 714.1 + 41.5 OR 714.0 + 336.3, 336.8, 336.9, 344.0–344.5, or 344.9 OR 714.0 + 81.41 from 1983 to 1989; 81.54 or 81.55 from 1990 to 2001
Alderman et al., 2002 [112] US 1996–1997	Nationwide Inpatient Sample (release 5 and 6)	Visit coded with ICD-9 714 + at least 1 of the following ICD-9 codes specific for procedures for the hand: 81.25–81.28 or 81.71–81.75 or 82.33 or 83.42
Hootman et al., 2002 [113] US 1997	1997 National Ambulatory Medical Care Survey (NAMCS) and the 1997 National Hospital Ambulatory Medical Care Survey (NHAMCS)	Non-injury ambulatory care visit with a primary provider diagnosis of arthritis or other rheumatic condition as coded with ICD-9-CM 714
Griffiths et al., 2001 [114] US 7/1993–2/1998	Unspecified US managed care database comprising plans in the eastern and midwestern US	ICD-9-CM diagnosis code 714.XX during 6 months prior to or in the first month of DMARD therapy, age 18 years or older at the time the first DMARD observed was prescribed, any oral or injectable DMARD therapy prescribed for 2 or more consecutive months during enrollment in the plan in study period, and at least 6 months of DMARD-free enrollment in the plan in study period, prior to initiating DMARD therapy
Maclean et al., 2001 [115] US 1991–1995	Data from unspecified national health insurance company (eligibility, claims & pharmacy claims files)	Required at least 2 physician visits > 2 months apart with an RA diagnosis code (ICD-9: 714, 714.0, 714.1, 714.2, 714.4, 714.8, 714.81, 714.89)
Walsh et al., 2000 [116] US 1995	National Center for Health Statistics—Selected Causes of Death	Female + ICD-9 code 714.0–714.2
Rosenman et al., 1995 [117] US 1990–1991	Michigan hospital discharge data	Age 20 or over + ICD-9 714 + 500 or 501 or 502 or 505
Gridley et al., 1994 [118] US 1/1969–9/1990	US Veterans Affairs discharge records	Age at least 18 years + ICD8 code 712.1 or ICD-9 714.1 + no cancer diagnoses prior to index visit or death during index visit

[a] Related studies.

[b] *Note*: These studies often sought cases of RA in addition to other diagnoses/procedures, e.g., RA in pregnancy, RA in patients undergoing hip replacement. See Appendix C (online) for definitions of all codes.

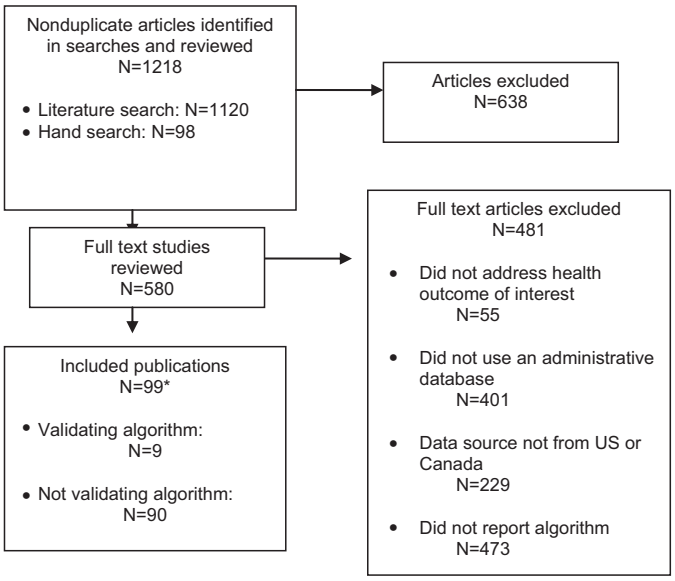

Fig. 1. Disposition of studies located for review.

the International Classification of Diseases, Ninth Revision (ICD-9) code 714 (without specifying extensions) and the relative benefit of adding laboratory and pharmacy data [14]. Between January 2001 and July 2002, 737 patients were seen at the VA rheumatology clinic. After selecting a random sample of 252 patient charts, the researchers identified 184 that included at least two rheumatology clinic visits >6 weeks apart. Of the remaining 68 patients in the random sample, 10 contained fewer than two rheumatology notes and 58 had unavailable medical records. Two reviewers examined the charts to identify patients meeting the gold standard for diagnosis (two visits to see a rheumatologist for RA care at least 6 weeks apart), and captured data on the ACR criteria for RA as well. Eighty-six cases met the gold standard. Ninety-two percent of patients who met the gold standard definition also fulfilled four or more criteria from the American College of Rheumatology (ACR) [15]. The chart-verified cases were then used as the gold standard to calculate the value of ICD-9 code 714, the presence of a DMARD prescription in the pharmacy record, and a positive rheumatoid factor (RF) titer, as well as combinations of these data points.

The use of ICD-9 code 714 alone resulted in 100% sensitivity, but 55% specificity. All false positives did have a rheumatic disease diagnosis of some sort, as would be expected given that the patient source was limited to a rheumatology clinic. The addition of either the pharmacy data on DMARD prescription or of clinical RF titer data substantially improved the specificity over the 714 code alone, with some loss of sensitivity. With the addition of DMARDs, specificity was 83% and sensitivity 85%; with RF titer, the specificity was 88%, and the sensitivity was 91%. The positive predictive value was highest when all three measures were combined, yielding a positive predictive value of 97% [14]. The ROC curve was used to assess tradeoff of sensitivity and specificity; the best measure was a combination of ICD-9 code 714 and positive RF titer, with an area under the curve of 0.90.

Similarly, Medicare claims data were used in a study of patient records from eight rheumatology offices in three states. Using Medicare part B, physician claims, from Massachusetts, Colorado and Virginia, Katz et al. examined an algorithm that included ICD-9 codes 714.0, 714.1, 714.2, 714.3, 713.30, 714.31, 714.32, and 714.33 and Common Procedural Terminology (CPT) codes related to joint and soft tissue injection and aspiration (20550, 20600, 20605, 20610) [16]. Assessing Medicare claims against the presence of one of these codes in the medical records, with the requirement that the visit dates be within 2 days of each other yielded a sensitivity of 90% (95% CI: 0.85–0.95) and a PPV of 95% (95% CI: 0.92–0.98) [16]. The sensitivity for the performance of the CPT codes was 85% (95% CI: 0.78–0.93) and PPV was 96% (95% CI: 0.90–1.0). This study also did not have access to pharmacy data.

A study from Liao et al. [17] assessed the relative value of codified data (that entered in structured format) and narrative, free text data in identifying cases of rheumatoid arthritis. This use of the complete electronic medical record (both coded and free text data) was an attempt to mitigate the previously noted high number of false positives that occur when relying only on ICD-9 coding. The initial study population comprised patients with at least one ICD-9 code for RA (714 plus all sub-codes) or evidence of having been tested for anti-CCP antibodies, selected from the initial 4 million patients in the health system. The data types being evaluated were ICD-9 codes, pharmacy data and laboratory values for anti-CCP and rheumatoid factor. To examine the value of narrative data, the investigators used health care provider notes, radiology reports, pathology reports, discharge summaries and operative reports. A training set of 500 randomly selected patients initially identified as having RA was used to develop the classification algorithm. Two rheumatologists reviewed medical records to identify those meeting the gold standard diagnosis, which required as a rheumatologist's diagnosis and supporting clinical data. Cases were defined as definite RA, possible/probable RA and not RA. Patients with definite RA were considered cases, and all others were controls. Of the 500 patients initially selected from those initially considered to have RA, 96 (19%) were confirmed as having RA. Once the algorithm was developed, it was tested in an additional validation set of 400 patients initially presumed to have RA.

The algorithm that was tested using only codified data available in an EMR included values for the ICD-9 code for RA (714.x), anti-TNF, RF positive, and methotrexate for positive predictors, with ICD-9 codes for JRA, systemic lupus erythematosus (SLE) and psoriatic arthritis (PsA) serving as negative predictors. The positive predictive value for this algorithm, was 89% (95% CI: 86%–93%), and it had a sensitivity of 56% (95% CI: 46%–66%). The authors also applied algorithms previously published using administrative data as comparisons. Three or more ICD-9 RA codes resulted in a PPV of 56% (95% CI: 47%–64%) and one or more ICD-9 RA codes plus at least one DMARD in pharmacy data had a PPV of 45% in this data set (95% CI: 37%–53%). Adding the free text from the EMR using natural language processing increased the PPV to 94% (95% CI: 91%–96%) [17].

In a study by Kim et al. [18] all patients were at least 65 years old, of low to moderate income and had possible financial hardship paying for medications. The investigators used three algorithms using the ICD-9 code 714 (without specifying extensions) to identify patients that could potentially have RA: (1) two claims with a diagnosis of RA (time period separating claims not specified); (2) three claims with a diagnosis of RA (time period separating claims not specified); and (3) two RA claims that were from a rheumatologist at least 7 days apart. A subgroup of patients also had filled a prescription for a DMARD in the year following an RA diagnosis. The gold standard was: (1) diagnosis of RA by a rheumatologist, or (2) fulfillment of the 1987 ACR classification criteria for RA, both identified via medical record review.

Of the 9482 patients originally identified with the algorithms, only 2% consented to have their medical records reviewed. PPVs ranged from 34% to 89% for the detection of RA. The highest PPV of 88.9% was calculated when assessing the use of two RA claims

from a rheumatologist, separated by at least seven days, along with a DMARD prescription in the year following RA diagnosis, against a gold standard of diagnosis by a rheumatologist. Similar to other studies in this review, this study demonstrated a clear benefit of using pharmacy data in addition to ICD-9 codes. The algorithm above without the DMARD requirement was associated with a PPV of only 66.7%. In addition, the predictive value of the coding scheme varied substantially by which gold standard was used. Depending on the gold standard, the optimal coding scheme resulted in PPVs ranging from 86.2% to 88.9%, although the confidence intervals all overlapped [18].

The accuracy of Medicare claims for RA within a selected population of total hip replacement recipients in Medicare was assessed by Losina et al. [19]. The gold standard was medical records examined by trained nurse abstractors, who searched the admission note, discharge note and operative note for indication of the diagnosis. Of note, they were restricted to the records from a single hospitalization, so diagnoses that occurred in physicians' offices, but that were not recorded in the hospital record would have been missed. Using ICD-9 codes 714 and 714.0 the investigators found a sensitivity of 65% and PPV of 86%. A further analysis comparing the accuracy of claims data in large and small hospitals found that sensitivity in low volume hospitals was higher (84%; 95% CI: 68%–100%) than in high volume hospitals (44%; 95% CI: 21%–67%) [19].

Using data from Northern California Kaiser Permanente, Klein et al. validated several computer case definitions of autoimmune diseases, including codes for JRA (714.30, 714.31, 714.32, 714.33) and RA (714.0, 714.1, 714.2, 714.81 and v82.10) and text write in diagnosis [20]. Using a strict gold standard definition, requiring two clearly stated diagnoses of JRA or RA with at least one by a rheumatologist, 47.1% of presumed JRA and 48% of presumed RA cases were confirmed.

Bili et al. used medical records in the Geisinger Health System as part of a study of hydroxychloroquine in reducing diabetes risk to verify a random sample of patients identified as having had a code of 714.0 at 2 outpatient encounters with a rheumatologist. Of the 100 patients presumed to have RA, 97 were confirmed using the 1987 ACR classification criteria as the gold standard [21]. In an insurance company-based study by MacLean et al., the use of 2 or more diagnosis codes for RA with at least 30 days between the two visits yielded a PPV of 92%, but in this case the gold standard was based on a mailed survey [22].

Although they did not develop a new algorithm de novo, Carroll et al. assessed the portability of the algorithm developed by Liao et al. at Partners Healthcare [17] to locate cases in subsets of two disparate electronic health record (EHR) systems (Vanderbilt University, Northwestern University) in its original form and after expansion of the algorithm using specific disease and drug attributes (e.g., exposure to methotrexate, positive RF titer, presence of erosions) [23]. Because the Carroll et al. algorithm depends on the use of natural language processing at the individual sites, this analysis does not specifically meet inclusion criteria. Nonetheless, it provides some insight into issues of portability and the ability of computer based algorithms to work for identifying RA. When the original Liao algorithm was applied to these datasets, the PPV in the Vanderbilt set was 95% and sensitivity was 57%. For Northwestern, the PPV of the original algorithm was 87% and sensitivity was 60%.

Table 3 presents a list of studies that included algorithms to define the presence of RA but did not describe methods for confirming cases. Most algorithms ($n = 86$) relied on the presence of claims listing ICD-9 codes 714.x, or specific sub-codes, and several required the use of medications used to treat RA ($n = 31$). A number of studies ($n = 34$) also required more than one encounter coded for RA.

4. Discussion

Studies assessing the validity of coding algorithms for RA reported PPVs that ranged from 34% [18] to 97% [14], reflecting the effects of coding accuracy (including physician experience with diagnosis of the disease [24]), variation in populations, range of approaches, algorithms, and gold standards. All but one study [22] used the medical record to identify the gold standard, but the gold standard definitions differed in important ways, including the requirement in some studies that the diagnosis be made by a rheumatologist [18,20,21]. The highest PPVs [14,16,21] were obtained in studies that included two or more ICD (including code 714) or procedure codes and required the use of data on prescriptions or included narrative text or laboratory data from electronic medical records. The use of ICD-9 codes alone resulted in notably low positive predictive values [18,20,23]. As expected, more strict requirements, such as need for inclusion of medications and/or need for a visit by a rheumatologist, increased the specificity and the positive predictive value of the algorithms, but decreased the sensitivity.

The highest PPVs (95%–97%) were obtained in rheumatology clinics [16,21]. This is unsurprising because the prevalence of cases would be highest in these clinics, and may suggest that the coding schemes and associated validity could lack applicability to a more general clinical population. Indeed, all algorithms in non-rheumatology specific clinical populations demonstrated lower sensitivity and positive predictive values, although the requirements that claims be associated with a visit with a rheumatologist, and addition of pharmacy data, improved reported PPV in general. It is possible that the reasons for the additional value of these parameters differ and are associated with different patient populations.

Currently, patients with RA are treated early and aggressively; thus the use of algorithms that incorporate drugs will likely identify a broad spectrum of patients, including those with early disease and those with less severe disease. Conversely, algorithms that include visits to a rheumatologist may have a very high positive predictive value, but may select only patients with more severe disease. The use of laboratory tests, such as seropositivity for rheumatoid factor or anti-CCP, was associated with higher PPVs; but these algorithms are likely to select patients with worse prognosis, and dependence on laboratory tests could miss cases, given that at least 20 percent of patients are seronegative [25].

One study was able to assess negative predictive value and specificity [14]. With a 34% false positive rate, the use of ICD-9 coding alone was clearly not optimal for identifying RA, although sensitivity was 100%. Of note, this study was also conducted in patients from a rheumatology clinic; the known higher prevalence of RA in this clinical scenario would lead to a higher PPV than would be observed in databases from a general clinical population.

Although the search was extensive, this review has some limitations for current practice. First, the review was limited to studies conducted in the U.S. and Canada in light of the FDA's focus on conducting subsequent studies limited to North America. Second, recently the ACR and the European League Against Rheumatism (EULAR) published a new set of criteria to classify RA [26,27]. These criteria allow for earlier identification of cases of RA that would not have been identified as such in the studies included in our review. Thus, prevalence is likely to be higher in future studies, with a potential concomitant increase in PPV. Third, some studies preceded widespread use of newer tests such as anti-CCP and from increasingly used imaging techniques, such as magnetic nuclear resonance and ultrasound [28], which may also result in greater sensitivity for diagnosis, and higher prevalence and thus PPV.

In conclusion, there have been substantial efforts to propose and validate algorithms to define RA in automated databases from different populations. Algorithms that require a code from more than

one encounter and incorporate medications (e.g., DMARDs such as methotrexate or anakinra) or laboratory data (e.g., RF titers, anti-CCP) and/or required a diagnosis by a rheumatologist are associated with higher PPVs but may be identifying different and sometimes selected patient populations.

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Authorship statement

All authors declare that they have participated in: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version submitted.

Conflict of interest

The authors have no conflicts to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.03.075.

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