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Evaluation of the Effect of Diabetes on Rheumatoid Arthritis–related Outcomes in an Electronic Health Record–based Rheumatology Registry

Huifeng Yun[1], Fenglong Xie[1], Lang Chen[1], Shuo Yang[1], Leticia Ferri[2], Evo Alemao[2], and Jeffrey R. Curtis[1]

ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) who also have diabetes mellitus (DM) might have worse clinical outcomes and adverse events compared to patients with RA who do not have DM. We evaluated the effects of DM on Health Assessment Questionnaire (HAQ) changes and outpatient infection rates in patients with RA.

Methods. Using the American College of Rheumatology's Rheumatology Informatics System for Effectiveness (RISE) electronic health record–based registry, we identified patients with RA who had ≥ 1 rheumatologist visit with a HAQ measured in 2016 (index visit), ≥ 1 previous visit, and a subsequent outcome visit with the same HAQ measured at 12 months (± 3 months). We identified DM by diagnosis codes, medications, or laboratory values. Outpatient infection was defined by diagnosis codes or antiinfective medications. We calculated mean HAQ change and incidence rate (IR) of outpatient infections among patients with and without DM. Generalized linear models and Cox regression were used to calculate the adjusted mean HAQ change and HRs.

Results. We identified 3853 RA patients with DM and 18,487 without DM. The mean HAQ change between index and outcome visit among patients with DM was 0.03 and without DM was 0.002 ($P < 0.01$). We identified 761 outpatient infections for patients with DM with an IR of 22.6 (95% CI 21.0–24.2) per 100 person-years and 3239 among patients without DM with an IR of 19.8 (95% CI 19.1–20.5). The adjusted HR of outpatient infections among patients with DM was 0.99 (95% CI 0.91–1.07), compared to patients without DM.

Conclusion. Patients with RA with concomitant DM had greater worsening, or less improvement, in their functional status, suggesting additional interventions may be needed for RA patients with DM to optimize treatment and management of other comorbidities.

Key Indexing Terms: diabetes, disability, health assessment questionnaire, infection, registry, rheumatoid arthritis

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[1]H. Yun, PhD, F. Xie, PhD, L. Chen, PhD, S. Yang, MS, J.R. Curtis, MD, MPH, University of Alabama at Birmingham, Birmingham, Alabama; [2]L. Ferri, MD, PhD, E. Alemao, PhD, Bristol Myers Squibb, New York, New York, USA.

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Address correspondence to Dr. J.R. Curtis, 510 20th Street South, Birmingham, AL 35294, USA. Email: jrcurtis@uabmc.edu.

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Comorbidities complicate the course of rheumatoid arthritis (RA) and have become major concerns among patients with RA.[1,2] The more comorbidities a patient has, the more challenging it may make diagnostic and treatment decisions, and the greater chances of hospitalization and mortality.[3] On average, patients with RA have approximately 1.6 comorbidities.[4] Diabetes mellitus (DM), cardiovascular disease, infections, obesity, and cancer all have great effect on RA-related outcomes, and also affect risk for hospitalization, work disability, medical costs, quality of life, and mortality.[3,5] The accurate assessment of comorbidities is also an important topic, since some data sources might appreciably underascertain certain comorbidities.

As DM is one of the major comorbidities that patients with RA could have, some evidence suggests that patients with RA who also have DM may be more likely to have worse clinical outcomes and more adverse events (AEs) compared with patients with RA without DM.[6] Through several mechanisms, RA and DM have a common pathway as inflammation may cause insulin

resistance and DM. DM may also increase risk for AEs such as infection.[7,8] Given known associations between DM and risk of infections and other AEs, studies have shown that patients with RA and DM were less frequently under rheumatological care and receiving disease-modifying antirheumatic drug (DMARD) treatment, but more likely to be hospitalized for a longer period compared to patients without DM.[6]

To evaluate the effect of DM on RA-related outcomes, reliable data sources and proven approaches for identification of DM and RA-related outcomes are necessary. Although numerous studies have examined the association between DM and RA-related conditions, many of them have been limited to smaller cohorts or administrative claims data analysis. Small cohorts usually do not have the statistical power to evaluate key associations and to control for the full spectrum of potential confounders. Due to the lack of detailed information about RA and DM-related clinical factors, administrative data analyses have focused mainly on safety events rather than clinical outcomes. Considering the extensive data available in electronic health records (EHRs) and compared to previous studies using other types of data, analysis of EHR data has the potential to better assess the effect of DM on RA.[9] Whereas EHR data might be expected to have richer information (e.g., glucose levels, glycosylated hemoglobin [HbA1c], and RA disease activity) than claims data, limitations inherent to EHR-based data sources yield uncertainty as to the feasibility and suitability of EHR data to study comorbidities such as DM. This might be of particular concern if data from only a single specialty (e.g., rheumatology) is available, given that rheumatologists may be unlikely to code DM or record related information since DM is typically managed by primary care physicians or other specialists. Therefore, as an example of a comorbidity rarely directly managed by rheumatologists, but which has an important influence on outcomes in rheumatology patients, DM was selected as a high-value target to study in the context of concurrent RA in a single-specialty data source.

Since the effects of DM on patients with RA are likely to be multifaceted, and to better understand the profile and outcomes of RA patients with DM in a unique, single-specialty EHR data source, the objectives of the current study were (1) to identify RA patients with concomitant type 2 DM using a national rheumatology-based EHR registry; (2) to evaluate the association between type 2 DM and change in physical function as measured by the Health Assessment Questionnaire (HAQ) and its variants among RA patients with DM compared to RA patients without DM; and (3) to identify outpatient infections in EHR data, and then compare the risk of outpatient infection in RA patients with and without DM.

METHODS

Data source. We conducted a retrospective cohort analysis using January 2016 to June 2017 data from the American College of Rheumatology's (ACR) Rheumatology Informatics System for Effectiveness (RISE) EHR-based national registry. RISE passively collects data from EHRs of participating rheumatology practices, provides advanced measurement and data analytic capacities, and fulfills national quality reporting requirements.[10] RISE is governed by multiple institutional review boards, and individual patient consent for data collection, aggregation, and analysis is not required. The University of Alabama at Birmingham institutional review board approved the study for this analysis (IRB-300000748).

Study population. We required eligible patients to meet the following criteria: (1) ≥ 1 rheumatologist visit in 2016 with a valid HAQ measurement (index visit); (2) ≥ 1 RISE visit prior to the index visit; (3) ≥ 1 rheumatologist diagnosis code for RA (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM)] 714.0, 714.2, and 714.81, and ICD, 10th revision, Clinical Modification [ICD-10-CM] M05.* or M06.*, excluding M06.4) on or before the index visit; (4) ≥ 1 rheumatologist visit with a measurement of HAQ or 1 of its variants (of the same type as baseline) approximately 12 months (± 3 months) after the index visit (follow-up visit); and (5) aged ≥ 18 years on the index visit.[11] A valid HAQ measurement was defined as paired data at both baseline and follow-up for the 20-item HAQ, HAQ-II, 8-item modified HAQ (mHAQ), or 10-item multidimensional HAQ (MDHAQ). To increase the homogeneity of patient characteristics and reduce potential confounders, we further restricted the study population by excluding patients who had ≥ 1 type 1 DM diagnosis code (ICD-9-CM: 250.*1 or 250.*3; ICD-10-CM: E10*) on or before the index date, had a history of other autoimmune disease (ICD-9-CM: 555.*, 556.*, 696.*, or 720.; ICD-10-CM: K50*, K51*, L40*, L41*, L42, M45*, or M46*), or had a history of cancer (ICD-9-CM: 140.*–239.*, excluding 173.*; ICD-10-CM: C00*–D48*, ignoring nonmelanoma skin cancer). Because DM medications were used in part to satisfy the definition for this condition, and because not all are specific for DM, we excluded women who used metformin with a concomitant diagnosis for polycystic ovary syndrome (ICD-9-CM: 256.4 and ICD-10-CM: E28.2) on or before the index date, but had no diagnosis for DM. Follow-up time started at the index visit and ended at the visit with a valid physical activity measurement of the same type as at baseline, measured closest to 12 (± 3) months later (see Supplementary Figure 1, available with the online version of this article, for study design).

Identifying patients with DM. Using all available data prior to the index visit, we identified DM based on at least 1 ICD-9-CM or ICD-10-CM diagnosis code (ICD-9-CM: 250.*0 or 250.*2; ICD-10-CM: E11*), any prior prescription medication for DM or elevated DM laboratory value (HbA1c ≥ 6.5% [48 mmol/mol], random glucose > 200 mg/dL [11.0 mmol/L], or fasting glucose ≥ 126 mg/dL [7.0 mmol/L]). DM was classified as dichotomous (yes vs no) as of the index date based on all preceding data. Prescribed medications indicated for DM included α-glucosidase inhibitors, amylin analogs, biguanides, bile acid sequestrants, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, insulin, meglitinides, sodium–glucose cotransporter 2 (SGLT2) inhibitors, sulfonylureas, and thiazolidinediones (TZDs). Because we required only 1 prior visit in 2016 before the index date could occur, and as an exploratory analysis, we descriptively characterized how the prevalence of DM might change as additional RISE data over time were available. We evaluated the hypothesis that more visit data would increase the likelihood of identifying DM until DM prevalence became asymptotic. This important feature of the analysis helped inform the definition of how long the "baseline" period should be, quantified as the number of RISE visits.

Outcomes. The primary outcome of interest was the change in HAQ between the index visit and the outcome visit, occurring at approximately 12 months (± 3 months) after the start of follow-up. The same type of HAQ was required at both the index and outcome visit (e.g., if HAQ was used for the baseline, HAQ would be required at the outcome visit for that patient). However, for presentation purposes, all HAQ variants were normalized to a 0–3 scale. The secondary outcome assessed during the 1-year follow-up period was outpatient infection, defined as any diagnosis of infection (using ICD-9-CM or ICD-10-CM diagnosis codes) or prescribed antiinfective medication (identified using National Drug Codes for outpatient pharmacy prescriptions and Healthcare Common Procedure Coding System codes for medical procedures for parenteral antibiotics).

Covariates. All baseline covariates were measured using all available data

prior to or on the index date. Covariates that were selected based on potential associations with HAQ change or outpatient infections included age, sex, race, BMI, practice size, history of RA drug use, RA drug addition during follow-up, baseline RA disease activity measurement (classified as remission, low, moderate, and high using Routine Assessment of Patient Index Data 3 [RAPID3] and Clinical Disease Activity Index [CDAI]), comorbidities, and concurrent medications. The history of RA medication use included a count of the number of prior conventional synthetic disease modifying antirheumatic drugs (csDMARDs), tumor necrosis factor inhibitors (TNFi), and non-TNFi biologics. csDMARDs included methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine. TNFis included adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab; and non-TNFis included abatacept (subcutaneous [SC] and intravenous [IV]), tocilizumab (SC and IV), rituximab, and tofacitinib (an oral targeted synthetic DMARD, grouped with bDMARDs for this analysis). RA drug addition or switch during follow-up was examined between the index and the outcome visit and was categorized as never added, added exactly once, added exactly twice, and added ≥ 3 times. Comorbidities included diagnosis for depression, fibromyalgia, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), hyperlipidemia, myocardial infarction (MI), renal disease, peripheral vascular disease, retinopathy, and neuropathy. Given the typical pattern of prescribing data observed in RISE, concurrent medications were examined using the 16 weeks of data prior to the index visit and included nonsteroidal antiinflammatory drugs, narcotics, glucocorticoids (GCs), and antidepressants. Potential factors that might mediate the association between DM and outcomes were not included in the statistical analysis, such as CAD, hyperlipidemia, MI, and renal disease.

Statistical analysis. Standardized mean differences (SMDs) were used to compare baseline characteristics of patients with RA, comparing patients with and without DM. Baseline was defined using all available data prior to the index visit and SMDs ≥ 0.10 were considered potentially important.[12] We calculated mean HAQ change between the index and follow-up visit, stratified by HAQ category at the index visit (HAQ score: 0 to 0.5, 0.5 to < 1, and 1 to 3), due to the expectation that the baseline HAQ value would be an effect modifier of the subsequent change in HAQ, based on our prior work.[13]

Generalized linear models were used to calculate the adjusted mean HAQ change, controlling for potential confounders, including demographics and csDMARDs and bDMARDs. Venn diagrams were generated to evaluate the extent of overlap between the 3 criteria for DM (ICD-9-CM and ICD-10-CM diagnosis codes, laboratory results, and medications) and the 2 criteria for outpatient infections (diagnosis and medications).

We calculated the incidence rates (IRs) of outpatient infections per 100 patient-years among patients with and without DM and compared HRs using Cox regression adjusting for age, sex, race, and a variety of covariates.

RESULTS

Among 457,950 patients in the RISE registry at the time of analysis, we identified 120,270 patients who had at least 1 rheumatologist visit with a valid HAQ measure (Figure 1). After applying additional inclusion and exclusion criteria, we identified 3853 RA patients with DM (17.2%) and 18,487 without DM (82.8%), comprising the final analysis cohort of 22,340 patients.

With respect to the classification of type 2 DM, 90% of RA patients with DM were identified by DM medications, 32% by diagnosis codes, and 28% by laboratory tests; 60% of patients were identified using only 1 of these 3 types of data (Figure 2). Similarly for outpatient infections, the medication data was more informative than diagnosis code data; 74% of patients were identified by prescriptions for antiinfectives and 43% by diagnosis codes (data not shown). Using all 3 types of data, the prevalence of DM stabilized after 2 RISE visits in 2016 (Figure 3),

Baseline characteristics of RA patients with and without type 2 DM are presented in Table 1. Compared with RA patients without DM, RA patients with DM were likely to be older, have higher BMI, have a higher frequency of comorbidities, and use more opioids, antidepressants, statins, and other antihyperlipidemia medications. Among patients with DM, 59.1% used biguanides, 32.6% used insulin, 11.3% used DPP-4 inhibitors, 6.6% used GLP-1 receptor agonists, 3.9% used bile acid sequestrants, and 3.7% used SGLT2 inhibitors (Table 2). Among patients who had RAPID3 or CDAI values reported, patients with DM were more likely to be in moderate or high disease activity compared to patients without DM. During baseline, the most frequent index HAQ variant used was MDHAQ, followed by HAQ, HAQ-II, and MHAQ. The mean baseline HAQ value for patients with DM was 0.8 and for patients without DM was 0.7.

After stratifying by baseline HAQ score, patients with RA and DM further worsened slightly, or improved less, than patients without DM. HAQ change patterns of time varied depending on baseline HAQ score category, with patients who started doing relatively well (HAQ < 0.5) worsening, and those starting with high HAQ (1–3) improving (Table 3). Overall, the adjusted mean change in HAQ score between index and outcome visits among patients with DM was +0.03 (i.e., worsening) and among patients without DM was no change (0.002, $P < 0.01$). Factors significantly associated with greater worsening in HAQ included depression, fibromyalgia, COPD, and opioid use (Supplementary Table 1, available with the online version of this article).

Among those with DM, 761 outpatient infections were identified during 3371 person-years of follow-up, yielding an IR of 22.6 (95% CI 21.0–24.2) per 100 patient-years. For patients without DM, 3239 outpatient infections were identified with 16,392 person-years, yielding an IR of 19.8 (95% CI 19.1–20.5). After adjusting for age, sex, and race, the HR for outpatient infections among patients with DM compared with patients without DM was 1.17 (95% CI 1.08–1.27). However, after adjusting all potential cofounders, we did not observe any significant difference between patients with or without DM (Supplementary Table 2, available with the online version of this article).

DISCUSSION

In this analysis of data from a national US EHR-based rheumatology registry, we found that RA patients with concomitant type 2 DM had greater worsening (or lesser improvement) in their functional status as measured by HAQ and its variants than RA patients without DM. The annualized differences for HAQ we observed were 0.03 to 0.04 units during the limited 1-year follow-up time. Although the magnitude of effect was small, this magnitude of annualized change would result in a HAQ difference in the RA patients with DM that would exceed the minimal clinically important difference (MCID) for the HAQ of 0.22 units[14,15] within 6 to 7 years. Whereas patients with RA and type 2 DM may have a higher risk of outpatient infection, we

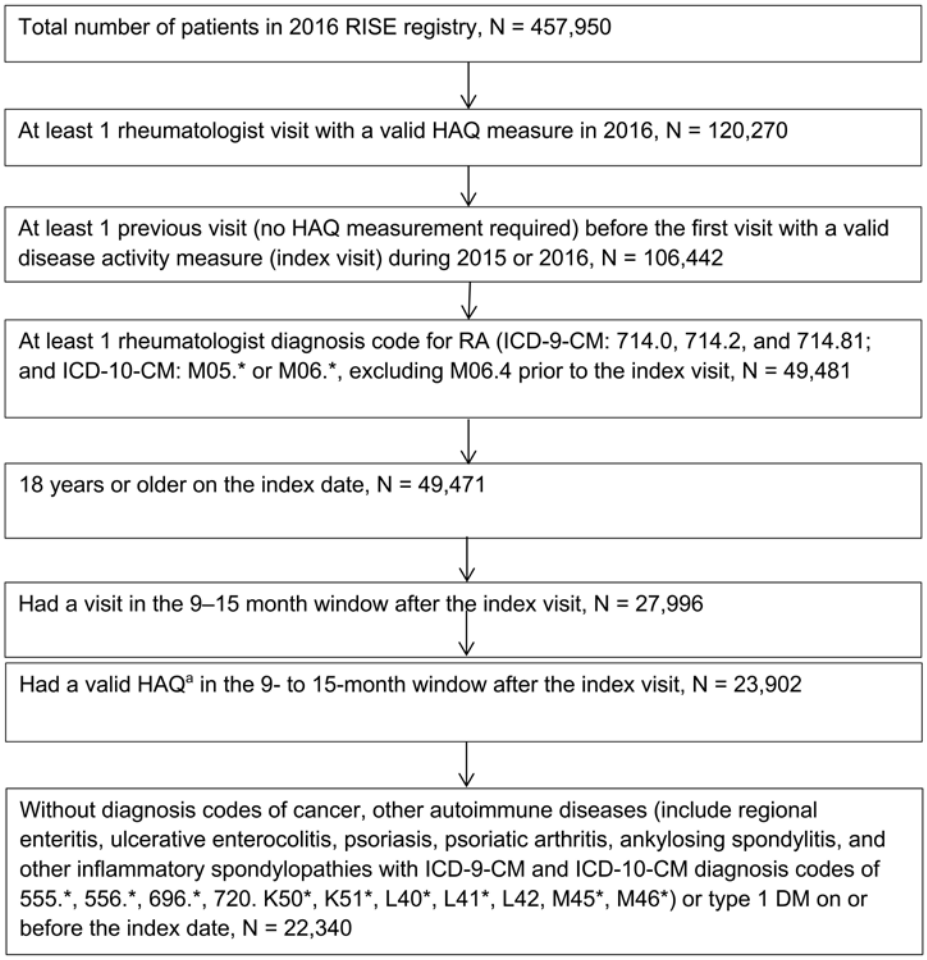

Figure 1. Attrition table describing study populations for primary and secondary analyses. [a]All HAQ variants were normalized to a 0–3 scale. Patients were required to have the same type of HAQ measured at both index visit and outcome visit. HAQ: Health Assessment Questionnaire; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; RA: rheumatoid arthritis; RISE: Rheumatology Informatics System for Effectiveness registry.

found that these differences were largely explained by a number of other differences that were imbalanced between RA patients with and without DM.

Importantly, and using DM as an example of a common comorbidity occurring in RA patients, we found that a single-specialty EHR was able to identify DM with reasonable prevalence, given it is not typically managed by rheumatologists. Indeed, most studies of multimorbidity in rheumatology patients have used administrative claims data or bespoke traditional registries, and the accuracy of identifying DM (or most other comorbidities) using a single-specialty or multispecialty EHR data system has been little studied. Although a couple of studies reported inconsistency of different sources of data for identifying the major comorbidities,[16,17] a previous study[18] developed a DM case-finding algorithm using encounter diagnoses, clinical history, pharmacy data, and laboratory results from a large public hospital system. With a reported positive predictive value of 90% and a sensitivity of 97%, this algorithm was based upon the gold standard of medical record review and applied point values for each criteria.[17,18] We did not have a gold standard for medical record review to assign these types of point values, but 90% of patients were receiving DM medications that are presumably more specific for DM than diagnoses. This observation was consistent with expectations, given that medication reconciliation (i.e., verifying at each visit all the medications that each patient is taking, even if not prescribed by the rheumatologist) is a national quality measure with an overall performance score of 95.8% in RISE[10] 2018 (and data on file from the ACR). Using the composite of all 3 data types (medications, diagnoses from encounters and problem list, and laboratory results), we identified 17.2% patients with RA as having DM, which is comparable to prevalence estimates from other RA cohorts.[6,19] We also found that beyond 2 visits, the prevalence of concurrent DM changed minimally, suggesting that 2 visits (i.e., an index visit and at least 1 preceding visit) is sufficient to identify a concomitant comorbidity like DM. We would point out that the ascertainment of DM was heavily dependent on the availability of DM-specific medications, which as part of this quality

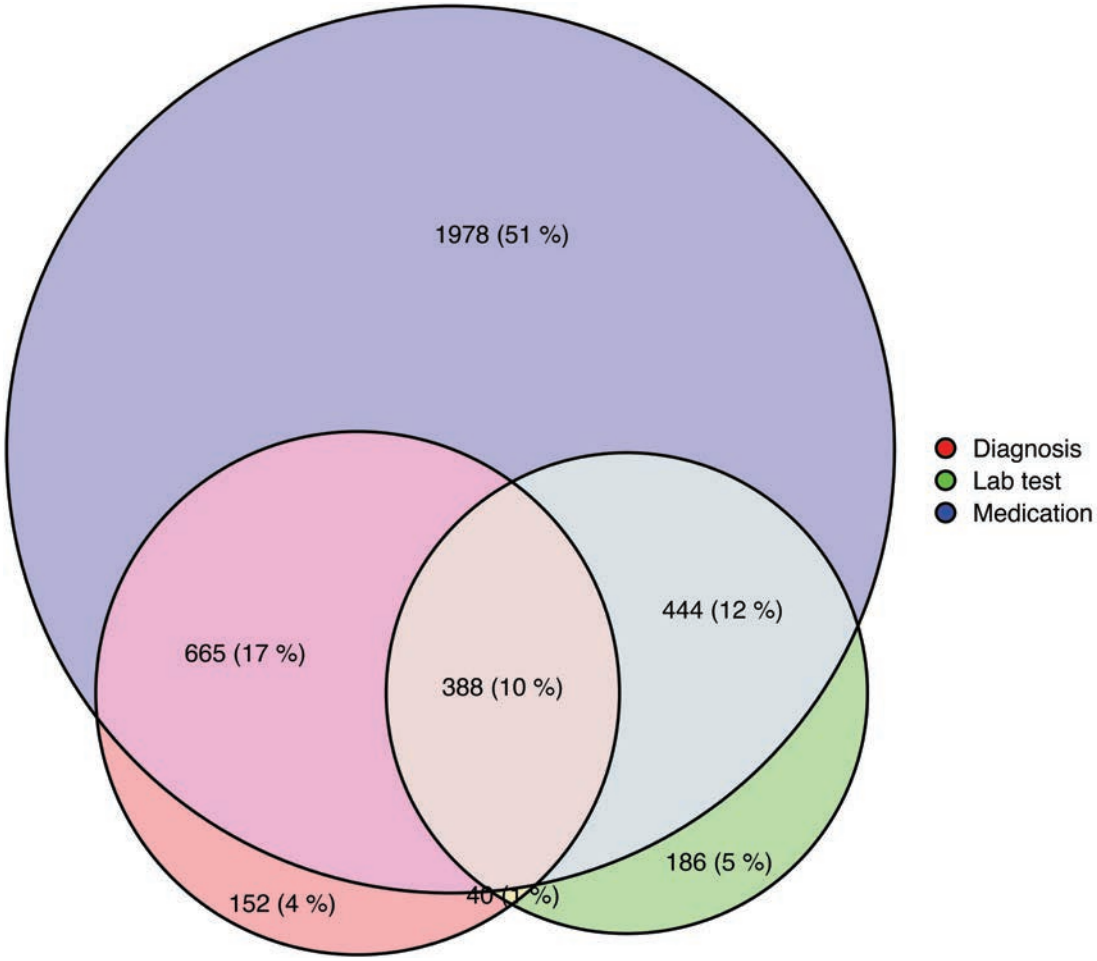

Figure 2. Number and percentage of eligible patients with RA identified as having diabetes using different sources of data (diagnoses, laboratory results, and diabetes medications). RA: rheumatoid arthritis.

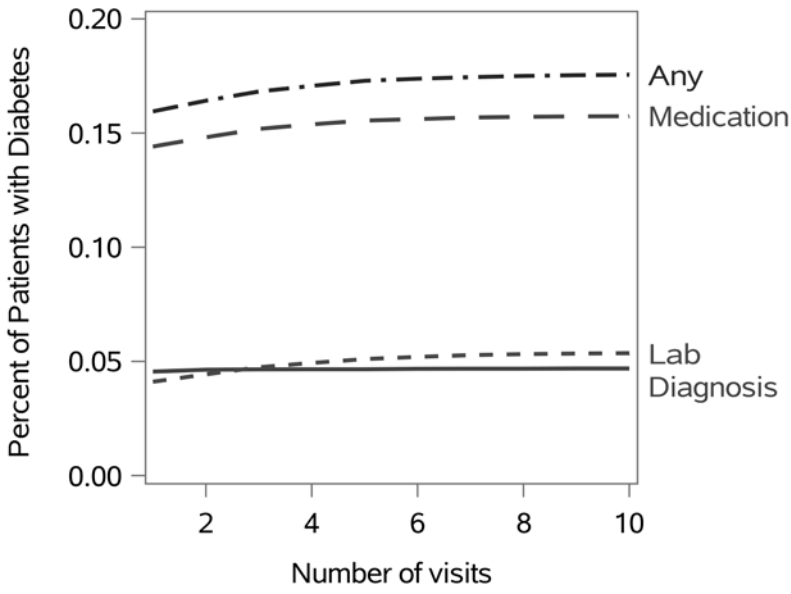

Figure 3. Total number of visits needed to identify diabetes in RISE registry. RISE: Rheumatology Informatics System for Effectiveness.

Table 1. Baseline characteristics of RA patients with and without diabetes.

	With DM, n = 3853	Without DM, n = 18,487	SMD
Median interval of baseline data available in days, median (IQR)	831 (557–1630)	742 (458–1462)	**0.15**
Median time of follow-up, days, median (IQR)	363 (332–381)	363 (330–381)	0.01
Age, yrs, mean (SD)	65.2 (11.4)	62.2 (13.6)	**0.24**
Age, yrs, n (%)			
< 50	349 (9.1)	3131 (16.9)	**0.24**
50–64	1366 (35.5)	6909 (37.4)	**0.24**
≥ 65	2138 (55.5)	8447 (45.7)	**0.24**
Sex, n (%)			
Female	2843 (73.8)	14,430 (78.1)	0.10
Male	1010 (26.2)	4057 (21.9)	0.10
Race, n (%)			
White	2439 (63.3)	13,044 (70.6)	**0.15**
Black	498 (12.9)	1496 (8.1)	**0.15**
Other	268 (7.0)	1227 (6.6)	**0.15**
NA	648 (16.8)	2720 (14.7)	**0.15**
Insurance coverage			
Medicare, n (%)	2328 (60.4)	8538 (46.2)	**0.29**
Medicaid, n (%)	235 (6.1)	612 (3.3)	**0.13**
Other insurance, n (%)	3348 (86.9)	15,879 (85.9)	0.03
Region, n (%)			
Midwest	814 (21.1)	4885 (26.4)	**0.12**
Northeast	111 (2.9)	730 (3.9)	**0.12**
South	2880 (74.7)	12,556 (67.9)	**0.12**
West	40 (1.0)	241 (1.3)	**0.12**
NA	< 10	75 (0.4)	**0.12**
BMI (mean (SD))	32.8 (7.4)	29.2 (6.7)	0.51
BMI, n (%)			
< 18.5	28 (0.7)	317 (1.7)	0.09
18.5–24.9	452 (11.7)	4823 (26.1)	0.09
25.0–29.9	1003 (26.0)	5839 (31.6)	0.09
30.0–34.9	1023 (26.6)	3886 (21.0)	0.09
≥ 35.0	1265 (32.8)	3194 (17.3)	0.09
NA	82 (2.1)	428 (2.3)	0.09
History of infection, n (%)	1776 (46.1)	7067 (38.2)	**0.16**
Comorbidity			
Depression	287 (7.4)	1045 (5.7)	0.07
Fibromyalgia	840 (21.8)	3108 (16.8)	**0.13**
COPD	256 (6.6)	784 (4.2)	**0.11**
Coronary artery disease	185 (4.8)	383 (2.1)	**0.15**
Hyperlipidemia	675 (17.5)	1794 (9.7)	**0.23**
Myocardial infarction	< 10	24 (0.1)	0.02
Renal disease	275 (7.1)	637 (3.4)	**0.17**
Peripheral vascular disease	103 (2.7)	477 (2.6)	0.01
Retinopathy	< 10	0 (0.0)	
Neuropathy	35 (0.9)	130 (0.7)	0.02
Practice size, n (%)			
Solo	165 (4.3)	986 (5.3)	0.05
2–4	354 (9.2)	1598 (8.6)	0.05
≥ 5	3334 (86.5)	15,903 (86.0)	0.05
Medication history			
NSAID	2938 (76.3)	13,676 (74.0)	0.05
Narcotics	2380 (61.8)	8739 (47.3)	**0.29**
GC	2737 (71.0)	12,559 (67.9)	0.07
Antidepressants	1734 (45.0)	6716 (36.3)	**0.18**
Statins	2228 (57.8)	5759 (31.2)	**0.56**
Other nonstatin cholesterol medication	869 (22.6)	1638 (8.9)	**0.38**

Table 1. Continued.

	With DM, n = 3853	Without DM, n = 18,487	SMD
csDMARD, current use[a]			
MTX	1586 (41.2)	7894 (42.7)	0.03
HCQ	610 (15.8)	3490 (18.9)	0.08
LEF	301 (7.8)	1341 (7.3)	0.02
SSZ	167 (4.3)	908 (4.9)	0.03
bDMARD, current use			
ADA	175 (4.5)	1121 (6.1)	0.07
ETN	210 (5.5)	1419 (7.7)	0.09
IFX	385 (10.0)	1562 (8.4)	0.05
CZP	81 (2.1)	409 (2.2)	0.01
GOL	101 (2.6)	413 (2.2)	0.03
ABA	250 (6.5)	1052 (5.7)	0.03
RTX	101 (2.6)	413 (2.2)	0.03
TCZ	165 (4.3)	667 (3.6)	0.03
Tofacitinib, current use, N (%)	91 (2.4)	441 (2.4)	0.00
History of csDMARD, ever			
MTX	2834 (73.6)	12,534 (67.8)	**0.13**
HCQ	1320 (34.3)	6671 (36.1)	0.04
LEF	703 (18.2)	2854 (15.4)	0.08
SSZ	418 (10.8)	2055 (11.1)	0.01
History of bDMARD, ever			
ADA	609 (15.8)	2965 (16.0)	0.01
ETN	655 (17.0)	3358 (18.2)	0.03
IFX	707 (18.3)	2711 (14.7)	0.10
CZP	194 (5.0)	868 (4.7)	0.02
GOL	193 (5.0)	804 (4.3)	0.03
ABA	567 (14.7)	2106 (11.4)	0.10
RTX	244 (6.3)	873 (4.7)	0.07
TCZ	344 (8.9)	1305 (7.1)	0.07
History of tofacitinib, ever, n (%)	197 (5.1)	920 (5.0)	0.01
History of csDMARD, bDMARD, or tsDMARD (as listed above)	3745 (97.2)	17,834 (96.5)	0.04
Drug switch during follow-up, n (%)			
Never	2398 (62.2)	11,493 (62.2)	0.00
Once	1112 (28.9)	5131 (27.8)	0.00
Twice	273 (7.1)	1471 (8.0)	0.00
≥ 3×	70 (1.8)	392 (2.1)	0.00

Values in bold indicate SMD > 0.1. [a]Identified using the 16 weeks of data prior to the index visit. ABA: abatacept; ADA: adalimumab; bDMARD: biologic DMARD; COPD: chronic obstructive pulmonary disease; csDMARD: conventional synthetic DMARD; CZP: certolizumab pegol; DM: diabetes mellitus; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GC: glucocorticoid; GOL: golimumab; HCQ: hydroxychloroquine; IFX: infliximab; LEF: leflunomide; MTX: methotrexate; NA: not available; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis; RTX: rituximab; SMD: standardized mean difference; SSZ: sulfasalazine; TCZ: tocilizumab; tsDMARD: targeted synthetic DMARD.

measure, are generally updated at every visit. In fact, we would expect that any comorbidity for which specific medications can reasonably serve as a proxy to identify the condition would be well ascertained in this type of single-specialty EHR registry. This might include, for example, COPD and asthma, where the use of bronchodilators and inhaled steroids are reasonably specific. Other examples might include hyperlipidemia or hypothyroidism. In contrast, comorbidities for which there are no specific medications would likely be much more difficult to accurately ascertain in this type of data source.

Although mechanisms are not clear, patients with RA have been previously shown to have higher prevalence of DM or insulin resistance compared to the general population, which may be in part related to a dysregulated immune system and/or medications used to treat RA (e.g., systemic GCs).[20,21] In addition, hyperglycemia might lead to systemic chronic inflammation through a multifactorial process, and may have a negative effect on skeletal muscle function.[22,23,24] Further, DM may increase the risk of disability through micro- and macrovascular complications, resulting in neuropathy and retinopathy, which are also responsible for the mobility limitations and falls among older adults with DM.[25,26] Thus, RA patients with DM had a

Table 2. Clinical characteristics of RA patients with and without diabetes.

	With DM, n = 3853	Without DM, n = 18,487	SMD
Diabetes-related indicators			
Diagnosis by ICD-9-CM/ ICD-10-CM, n (%)	1245 (32.3)	0 (0.0)	
Medications, n (%)			
Biguanide	2276 (59.1)	0 (0.0)	
Insulin	1256 (32.6)	0 (0.0)	
Sulfonylureas	832 (21.6)	0 (0.0)	
DPP-4 inhibitors	434 (11.3)	0 (0.0)	
GLP-1 receptor agonists	253 (6.6)	0 (0.0)	
TZD	213 (5.5)	0 (0.0)	
Bile acid sequestrants	151 (3.9)	0 (0.0)	
SGLT2 inhibitors	141 (3.7)	0 (0.0)	
Other	67 (1.5)	0 (0.0)	
Glucose, mean (SD)	141 (76.7)	95.9 (17.5)	**0.82**
Random glucose > 200 mg/dL (11.0 mmol/L), n (%)[a]	926 (24.0)	0 (0.0)	
HbA1c, mean (SD)	6.8 (1.3)	5.7 (0.4)	**1.12**
HbA1c > 6.5%, N (%)	300 (7.8)	0 (0.0)	
RAPID3, 0–30, n (%)			**0.27**
Remission, ≤ 3	417 (10.8)	3328 (18.0)	
Low, > 3 to ≤ 6	393 (10.2)	2309 (12.5)	
Moderate, > 6–12	722 (18.7)	3242 (17.5)	
High, > 12	1211 (31.4)	4044 (21.9)	
Missing	1110 (28.8)	5564 (30.1)	
CDAI, n (%)			**0.14**
Remission	206 (5.3)	1416 (7.7)	
Low	745 (19.3)	3921 (21.2)	
Moderate	535 (13.9)	2375 (12.8)	
High	313 (8.1)	1025 (5.5)	
Missing	2054 (53.3)	9750 (52.7)	
Index HAQ, mean (SD)	0.8 (0.6)	0.7 (0.6)	**0.22**
Index HAQ type, n (%)[b]			
HAQ	1496 (38.8)	6159 (33.3)	**0.11**
HAQ-II	155 (4.0)	723 (3.9)	**0.11**
MHAQ	266 (6.9)	1653 (8.9)	**0.11**
MDHAQ	1936 (50.2)	9952 (53.8)	**0.11**

Values in bold indicate SMD > 0.1. [a] Very few fasting glucose values were available in the RISE data that only random glucose values were shown. [b]All types of HAQ scores were normalized to a 0–3 scale. CDAI: Clinical Disease Activity Index; DM: diabetes mellitus; DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide-1; HAQ: Health Assessment Questionnaire; HbA1c: glycosylated hemoglobin; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; ICD-10-CM: International Classification of Diseases, 10th revision, Clinical Modification; mHAQ: modified Health Assessment Questionnaire; MDHAQ: 10-item multidimensional Health Assessment Questionnaire; RA: rheumatoid arthritis; RAPID3: Routine Assessment of Patient Index Data 3; RISE: Rheumatology Informatics System for Effectiveness registry; SGLT2: sodium–glucose cotransporter 2; SMD: standardized mean difference; TZD: thiazolidinedione.

higher disease morbidity and disability, but are less likely to be treated by rheumatologists than those without DM.[6] In studying patients with RA enrolled in the DANBIO registry (https://danbio-online.dk), patients with DM had poorer initial response to the RA treatment and lesser improvement in the Disease Activity Score in 28 joints based on C-reactive protein (DAS28–CRP) than RA patients without DM.[27] Among participants with RA in the FORWARD cohort, Michaud, *et al* found that HAQ progression was independently associated with baseline DM.[28] The annualized progression rates (HAQ difference of 0.006 units) for RA patients with DM were low (and smaller than the magnitude that we observed) but were significantly worse compared to RA patients without DM.[28]

Systemic inflammation and RA treatments may interfere with insulin resistance and the progress of DM, and then increase the disease burden for patients with RA through several mechanisms, including TNF-α and interleukin 6 related to insulin receptor blockade, and CRP and plasminogen activator inhibitor-1 associated with insulin sensitivity.[29,30] An increased risk of serious infection among patients with DM has been observed in previous research.[31] For example, using the medical and pharmacy administrative claims of a large US healthcare organization, a previous study reported that DM was independently associated with the risk of a bacterial infection.[32] However, our current study did not find a significant association with outpatient infections for DM and older patients. Although potential confounders might still exist, it is likely that outpatient infections are underascertained in this rheumatologist-only data source, given that the absolute incidence rates for infections that we found were seemingly lower than in other reports.[33] RISE does not capture hospitalized infections, and regardless of comorbidity, patients are likely to receive care from physician specialties other than rheumatologists for the treatment of outpatient infections. It is also possible that patients with severe DM, and who are older, might be less likely to visit their rheumatologist, and underascertainment of outpatient infections in RISE might be differential by these factors.[34]

Our study has limitations. Our cohort included RA patients whose rheumatologists participate in the national RISE registry, which is predominantly confined to community practice clinicians with minimal representation of academic medical centers. The data available are generally derived only from rheumatologists' EHRs, and therefore we may underestimate patients' baseline comorbidities that were not primarily managed by rheumatologists, although some of them have comparable proportions reported from different data sources.[35,36] Given the current longitudinal availability of RISE data, we required an outcome visit occurring at approximately 12 months (± 3 months) after the start of follow-up, but a 1-year HAQ change is short. We also recognize the potential for overadjustment for factors related to DM in our multivariable-adjusted results. The crude differences in HAQ change may have been as large as 0.06–0.08 units, providing an upper bound on the magnitude of differences related to DM. Last, the total number of patients with glucose values that were known to be fasting or nonfasting was very small compared to the total number of the random glucose values.

In conclusion, among patients with RA, this methods-focused analysis found a reasonable prevalence of DM, a comorbidity that rheumatologists typically do not manage and is predominantly identified through DM-specific medications. Those

Table 3. Change in HAQ score during follow-up among patients with or without diabetes, stratified by baseline HAQ.

Baseline HAQ Score Category	Crude Mean Change in HAQ		Adjusted Mean Change in HAQ Score		Adjusted[a] Mean Difference of Change in HAQ Score (95% CI) Between Patients With or Without Diabetes
	Patients With Diabetes	Patients Without Diabetes	Patients With Diabetes	Patients Without Diabetes	
0 to < 0.5	0.14	0.12	0.49	0.48	0.002 (–0.01 to 0.02)
0.5 to < 1	0.08	0.02	0.08	0.05	0.03 (0.01–0.06)
1–3	–0.23	–0.31	–0.31	–0.35	0.04 (0.00–0.08)

All HAQ variants were normalized to a 0–3 scale. Patients were required to have the same type of HAQ measured at both index visit and outcome visit. [a]Adjusted for age, sex, race, BMI, index HAQ score, insurance, comorbidities (e.g., depression, fibromyalgia, chronic obstructive pulmonary disease), medication history (e.g., history of NSAID use, history of opioids), current csDMARD, current bDMARD, and tofacitinib use (identified using the 16 weeks of data prior to the index visit). bDMARD: biologic DMARD; BMI: body mass index; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; NSAID: nonsteroidal antiinflammatory drug.

with concomitant DM (17% of total) had greater worsening (or lesser improvement) in their functional status as measured by HAQ and its variants. Although the magnitude of effect of DM on RA-related outcomes was small during the first year of follow-up, this change would exceed the MCID in HAQ of 0.22 units within 6 to 7 years, suggesting additional interventions may be needed for RA patients with DM to optimize treatment and management of elated comorbidities.

DATA AVAILABILITY

At this time, we are not able to provide this given the restrictions put in place by the ACR. However, we would be happy to answer questions or discuss thoughts with individuals who read the article.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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