Supplementing Claims Data with Electronic Medical Records to Improve Estimation and Classification of Rheumatoid Arthritis Disease Activity: A Machine Learning Approach

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Objective. Previous attempts to estimate rheumatoid arthritis (RA) disease activity using claims data only did not yield high performance. We aimed to assess whether supplementing claims data with readily available electronic medical record (EMR) data might result in improvement.

Methods. We used a subset of the Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study (BRASS) that had linked Medicare claims. The disease activity score in 28 joints with C-reactive protein (DAS28-CRP) was considered the gold standard of measure. Variables in the linked Medicare claims, as well as EMR recorded in the preceding one-year period were used as potential explanatory variables. We constructed three models: “Claims-Only,” “Claims + Medications,” and “Claims + Medications + Labs (laboratory data from EMR). We selected variables via adaptive LASSO. Model performance was measured with adjusted R2 for continuous DAS28-CRP and C-statistics for binary category classification (high/moderate vs low disease activity/remission).

Results. We identified 300 patients with laboratory data and linked Medicare claims. The mean age was 68 years and 80% were female. The mean (SD) DAS28-CRP was 3.6 (1.6) and 51% had high or moderate DAS28-CRP. For the continuous estimation, the adjusted R2 was 0.02 for Claims-Only, 0.09 for Claims + Medications, and 0.18 for Claims + Medications + Labs. The C-statistics for discriminating the binary categories were 0.61 for Claims-Only, 0.68 for Claims + Medications, and 0.76 for Claims + Medications + Labs.

Conclusion. Adding EMR-derived variables to claims-derived variables resulted in modest improvement. Even with EMR variables, we were unable to estimate continuous DAS28-CRP satisfactorily. However, in claims-EMR models, we were able to discriminate between binary categories of disease activity with reasonable accuracy.

INTRODUCTION

The ability to estimate rheumatoid arthritis (RA) disease activity would be a powerful tool for epidemiologic studies that lack direct disease activity measures such as the Disease Activity Score 28-

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Correction added on September 18, 2019 after first online publication: The Conclusion section of the Abstract has been updated to correct grammatical errors.
SIGNIFICANCE & INNOVATION
- Previous attempts to estimate rheumatoid arthritis (RA) disease activity using claims data only have been unsuccessful.
- We demonstrated that the use of simple electronic medical record (EMR) variables linked to claims data can moderately improve binary classification (high + moderate vs low disease activity + remission).
- Accurate estimation of continuous disease activity score proved to be difficult even with added EMR variables.
- Model-based classification, for example, can be used to examine treatment effect modification by disease activity categories.

METHODS

Participants. We utilized the Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study (BRASS), a single-center observational cohort of adults (older than 18 years) with prevalent RA cared for at Brigham and Women’s Hospital, which is an urban tertiary care teaching hospital (7). Over 1500 patients with confirmed RA by the 1987 ACR criteria (8) have been followed for more than 15 years with annual measurement of disease activity with the DAS28-CRP. Among these patients, we selected individuals with at least 1 year of linked Medicare administrative claims data preceding a disease activity measurement between 2006-2010, the years for which we had existing linked claims. Medicare is the U.S. public insurance for individuals older than 65 years and for a subset of younger individuals with disabilities (9). A subset of BRASS patients with linked Medicare data also had medication benefits through Medicare, known as Medicare Part D, and for these individuals, pharmacy dispensing data were available.

Dependent variables. BRASS recorded DAS28-CRP scores, a version of DAS28 with CRP as an inflammatory marker but without patient global health assessment on an annual basis (10). Each patient potentially had multiple DAS28-CRP measurements, but we focused on the first measurement during the follow-up to avoid correlated dependent variables within each individual, which could complicate the cross-validation process (11). We modeled disease activity in two ways: original continuous form and dichotomized form. We dichotomized the variable as “moderate or high disease activity” (DAS28-CRP at 3.2 or greater) and “low disease activity or possible clinical remission” (DAS28-CRP less than 3.2). We chose these cutoffs based on the treat-to-target strategy for established RA patients (12,13). We will refer to the dichotomized cutoff of 3.2 or greater vs. less than 3.2 as high/moderate vs. low disease activity, respectively, for the purposes of this study, recognizing differing perspectives regarding the definition of a DAS28-CRP cutoff for clinical remission.

Potential explanatory variables. We derived explanatory variables from three sources: Medicare claims data, Medicare Part D pharmacy dispensing data, and EMR data. From Medicare claims, we used ICD-9 codes to identify 26 variables, including demographics, comorbidities, joint replacement surgery, rehabilitation visits, number of RA-related codes, laboratory and imaging use, and health care utilization (See eTable 1 for codes). For a subset of patients, Medicare Part D claims provided medication information regarding biological and conventional disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, and opioids.

We used simple EMR-derived variables collected during routine clinical practice to supplement the claims-derived variables. We did not use variables that may not be available outside of our data sources, such as survey data collected for research purposes from the BRASS cohort. We extracted data via the Research Patient Data Registry (RPDR) (14–16), a centralized clinical data registry consisting of routinely collected data from the EMR. We obtained smoking status, body mass index (BMI), systolic blood pressure, medication use (when Medicare Part D was not available), laboratory abnormalities for RA seropositivity (rheumatoid factor or anticyclic citrullinated peptide), hematocrit, erythrocyte sedimentation rate (ESR), and CRP. When repeated measurements were avail-
able, laboratory abnormality was recorded if any one of the measurements was abnormal. Missing values were handled via the missing category method. For example, a laboratory variable was coded as either normal, abnormal, or missing. We did not pursue natural language processing of EMR free text because we aimed to develop a simple and potentially portable estimation and classification model of disease activity. Tender and swollen joint counts were not available as structured data in our system.

For both claims and EMR data sources, the variable assessment period was the 1-year period preceding the index date on which the first ever DAS28‐CRP was recorded in BRASS. This rule was applied to all variables, including relatively stable variables such as seropositivity. For medications, both ongoing therapy and new therapy were considered similarly as “ever use” within this 12-month window.

**Modeling strategy.** We utilized a form of supervised machine learning, adaptive least absolute shrinkage and selection operator (LASSO). LASSO is a penalized regression that prevents model overfitting by restricting the magnitude of coefficient estimates (regularization) and performs variable selection by setting some coefficient estimates to be zero (17,18). Adaptive LASSO (19) is an improvement upon the original LASSO, which allows a different penalty weight for each coefficient. Our modeling approach involved several steps: 1) initial coefficient estimation with ridge regression, 2) adaptive LASSO for variable selection, and 3) final modeling.

First, we obtained the absolute values of the ridge regression (20) estimates of coefficients. We constructed differential penalties based on the inverse of absolute ridge coefficient estimates (19). These differential penalties ensured that more promising potential explanatory variables were penalized to a lesser extent in the subsequent steps.

Second, we ran an adaptive LASSO for variable selection. The optimal value of the overall penalty term was chosen by minimizing 10-fold cross-validation errors. Importantly, cross-validation results can be dependent on the specific random split of the data when the data set is small. Therefore, we repeated 10-fold cross-validation 10,000 times to stabilize this process and to minimize randomness (21,22). We combined these 10,000 models by examining the number of times each variable was chosen, and we used variables selected in at least 60% of the adaptive LASSO model fits as the final set of variables, in keeping with prior literature (23).

Third, the final model was fit with multiple regression for DAS28‐CRP as a continuous DAS28‐CRP, or logistic regression for the dichotomized DAS28 classification (DAS28‐CRP 3.2 or greater vs DAS28‐CRP less than 3.2). We used adjusted $R^2$ to compare continuous DAS28‐CRP model fits. C-statistics were used to compare the ability of the binary DAS28‐CRP classification models to distinguish between high and low disease activity. We additionally calculated sensitivity, specificity, and correct classification rate at the threshold chosen by the Youden index (24) that aims to simultaneously maximize sensitivity and specificity. We used SAS v. 9.4 and R 3.4 [glmnet (25)] for computation.

For the candidate explanatory variables, we considered three increasingly larger potential variable pools to examine how simple EMR variables can improve estimation and classification based on claims variables only: 1) claims only (“Claims-Only”), 2) claims and EMR medications (“Claims + Medications”), and 3) claims, EMR medications, and laboratory values (“Claims + Medications + Laboratory Tests” Model). For EMR variables such as the laboratory test variables, we categorized values into the normal range and the abnormal range and incorporated missing as a category.

**RESULTS**

**Participants and characteristics.** We identified 300 adults with RA enrolled in BRASS with 1 year or more of linked Medicare claims preceding their initial DAS28‐CRP measurement between 2006‐2010. Thirty rheumatologists cared for these 300 patients. The distribution of patient cluster sizes was median 3.5 (interquartile range 1‐11). A subset of 95 patients had Medicare Part D medication coverage. Table 1 shows the patient characteristics at the initial DAS28‐CRP measurement. The mean age was 68 years, 80% were female, and 92% were white. The mean duration of RA was 21 years, reflecting the nature of the prevalent RA cohort that we were able to link to the Medicare claims. The extent of missingness in EMR data was as follows: BMI 13%, blood pressure (BP) 28%, smoking 12%, rheumatoid factor (RF) 36%, ESR 49%, CRP 19%, and hematocrit (5%). The mean (SD) of DAS28‐CRP was 3.6 (1.6). The disease activity categories were as follows:

| Variable | Result |
|----------|--------|
| n        | 300    |
| Age (Mean, SD) | 67.94 (9.72) |
| Gender - female (N, %) | 241 (80.33) |
| Race (N, %) | 276 (92.0) |
| white | 14 (4.8) |
| black | 10 (3.3) |
| other |        |
| DAS28-CRP (Mean, SD) | 3.58 (1.62) |
| DAS28-CRP Category (N, %) | 105 (35.0) |
| Clinical Remission | 41 (13.7) |
| Low Disease Activity | 93 (31.0) |
| Moderate Disease Activity | 61 (20.3) |
| High Disease Activity | 20.56 (13.28) |

Table 1. Patient characteristics at the first measurement of DAS28-CRP

Abbreviation: DAS28-CRP, Disease Activity Score in 28 joints with C-reactive protein; DMARD, disease-modifying antirheumatic drug.

| DMARDs (N, %)* | |
|---------------|---|
| 0             | 92 (30.7%) |
| 1             | 151 (50.3%) |
| 2             | 49 (16.3%) |
| 3             | 8 (2.7%) |

**RA Disease Duration (Mean, SD):** 20.56 (13.28)

*Number of unique DMARDs prescribed during the 1-year variable ascertainment period.
20% in high disease activity (more than 5.1), 31% in moderate disease activity (3.2–5.1), 14% in low disease activity (2.6–3.2), and 35% in clinical remission, here defined as less than 2.6.

Continuous DAS28-CRP estimation. Claims-only data resulted in a highly parsimonious final model with just two binary variables (Table 2). As a result, the proportion of
continuous DAS28-CRP explained \((R^2)\) was very poor at 0.03 (adjusted \(R^2 = 0.02\)). Models derived by an automated variable selection process may not be clinically interpretable. However, in this specific instance, the presence of laboratory tests (ever/never) for viral hepatitis and for CRP remained in the final model. CRP testing may be a surrogate for the need to assess inflammation formally, which is likely due to high disease activity. Viral hepatitis testing may herald the need to switch med-

### Table 3. Variable selection and final fit results for binary disease activity classification

| Data source          | Variable Selection | Coefficient | Selection | Coefficient | Selection | Coefficient |
|----------------------|--------------------|-------------|-----------|-------------|-----------|-------------|
|                      |                    |             |           |             |           |             |
|                     | (Intercept)        | 10 000      | 3.937     | 10 000      | 3.737     | 2.434       |
| Claims              | Number of outpatient visit | 0          | 0         | 0           | 0         | -           |
|                     | Number of ED visits | 5119        | -         | 0           | 0         | -           |
|                     | Length of hospitalization | 0          | 3520      | -           | 0         | -           |
|                     | Number of hospitalizations | 0          | -         | 0           | 0         | -           |
|                     | Number of chest X-ray | 110         | 2         | 0           | 0         | -           |
|                     | Arthrocentesis, yes/no | 5150       | 3858      | -           | 0         | -           |
|                     | ANA testing, yes/no | 636         | 745       | -           | 3         | -           |
|                     | BMD testing, yes/no | 0           | 0         | -           | 0         | -           |
|                     | CBC testing, yes/no | 118         | 2         | 0           | 0         | -           |
|                     | Anti-CCP testing, yes/no | 4893       | 4095      | -           | 9755      | -0.229      |
|                     | Metabolic panel, yes/no | 5174       | 7205      | -0.541      | 8709      | -0.460      |
|                     | HBV/HCV screening, yes/no | 9998       | 9999      | 0.210       | 10 000    | 0.571       |
|                     | Chest CT/MRI, yes/no | 5139       | 7305      | 1.306       | 9588      | 1.108       |
|                     | Liver enzymes, yes/no | 5142       | 7183      | 0.001       | 9540      | -0.184      |
|                     | Tuberculosis tests, yes/no | 5142       | 7183      | 0.001       | 9540      | -0.184      |
|                     | Age at DAS28-CRP | 0           | 0         | -           | 0         | -           |
|                     | CRP, yes/no | 9997       | -0.560    | 9999       | -0.801    | 10 000      | -0.720     |
|                     | RF, yes/no | 6           | 0         | -           | 0         | -           |
|                     | ESR, yes/no | 5192       | 7274      | -0.228      | 9583      | -0.173      |
|                     | Total Number of ESR/CRP | 0          | -         | 0           | 0         | -           |
|                     | Race, Black | 5640       | 8545      | 0.521       | 9428      | 0.307       |
|                     | Race, nonwhite/black | 79        | 21        | -           | 0         | -           |
|                     | Sex | 5034       | 5552      | -           | 8961      | 0.330       |
|                     | Charlson Comorbidity Index | 0        | -         | 0           | 0         | -           |
|                     | Joint surgeries, yes/no | 5703       | 7229      | 0.879       | 9799      | 0.729       |
|                     | Occupational therapy, yes/no | 5147       | 7220      | -0.285      | 9438      | -0.217      |
|                     | Physical therapy, yes/no | 0        | -         | 0           | 0         | -           |
|                     | Total Number of RA Codes | 0        | -         | 0           | 0         | -           |
| PartD/ EMR          | Total number of DMARD use | 7189      | -0.430    | 9501       | -0.422    | -           |
|                     | ever use of DMARD | 15         | -         | 0           | -         | -           |
|                     | ever use of glucocorticoids | 9999       | 0.232    | 10 000     | 0.216     | -           |
|                     | ever use of opioids | 9996       | 0.374    | 9772       | 0.144     | -           |
| EMR                 | BMI ≥30 | 0           | -         | 0           | -         | -           |
|                     | 25 ≤ BMI <30 | 7189       | -0.430    | 0           | -         | -           |
|                     | BMI <18.5 | 15         | -         | 0           | -         | -           |
|                     | BMI Missing | 9999       | 0.232    | 9562       | 0.450     | -           |
|                     | Systolic BP ≥160 | 9996       | 0.374    | 0           | -         | -           |
|                     | Systolic BP 120-159 | 5136       | -         | 0           | -         | -           |
|                     | Systolic BP missing | 10 000     | -0.773    | -           | -         | -           |
|                     | Smoking, current | 0           | -         | -           | -         | -           |
|                     | Smoking, past | 0           | -         | -           | -         | -           |
|                     | Smoking, missing | 22          | -         | -           | -         | -           |
|                     | RF abnormal | 10 000      | 0.579    | -           | -         | -           |
|                     | RF missing | 7948        | 0.393    | -           | -         | -           |
|                     | ESR abnormal | 10 000     | 0.442    | -           | -         | -           |
|                     | ESR Missing | 9624        | 0.839    | -           | -         | -           |
|                     | CRP abnormal | 9586       | 0.691    | -           | -         | -           |
|                     | CRP missing | 7480        | 0.167    | -           | -         | -           |
|                     | Hematocrit abnormal | 8793      | -0.216   | -           | -         | -           |
|                     | Hematocrit missing | -         | -         | -           | -         | -           |

Abbreviation: ANA, antinuclear antibody; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CBC, complete blood count; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; CT, computed tomography; DMARD, disease-modifying antirheumatic drugs; ED, emergency department; EMR, electronic medical record; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; Labs, laboratory test results; Meds, medications; MRI, magnetic resonance imaging; Part D, Medicare Part D prescription claims; RA, rheumatoid arthritis; RF, rheumatoid factor.

All variables including medications and laboratory results were as recorded within the 12-month period preceding the DAS28-CRP measurement.
ications, particularly to biological DMARDs in the setting of higher disease activity or inadequate disease control.

Adding four medication-related variables in the initial candidate variable pool (Claims + Medications) resulted in a much larger final model with 12 variables. The estimation performance was much better, although it still explained a relatively small fraction of continuous DAS28-CRP variability ($R^2 = 0.12$, adjusted $R^2 = 0.09$). Viral hepatitis and CRP testing remained in the final model again. Tuberculosis and liver enzyme testing, which may also precede biological DMARDs, were in the final model. Glucocorticoid use and opioid use made it to the final model, but not DMARD use. DMARD use might have been of little value because most patients in this tertiary care center RA cohort were on DMARDs.

Including further EMR variables (Claims + Medications + Laboratory Tests) resulted in a final model with 23 variables. The estimation performance improved further ($R^2 = 0.25$, adjusted $R^2 = 0.18$). Laboratory variables (CRP, ESR, RF, and hematocrit) exceeded the model inclusion threshold of 60%. For RF, CRP, and hematocrit, both the abnormal value indicator and the missing indicator remained in the model, meaning whether a measurement was made at all was also informative of the underlying disease activity in addition to the presence of an abnormal measurement.

### Binary category classification

Similar to the continuous DAS28-CRP estimation, the binary Claims-only model resulted in a final model with just two variables: the presence of CRP testing and joint surgery (Table 3). The area under the curve (AUC) of the model was 0.61 (Figure 1). At the optimal threshold that maximizes sensitivity and specificity jointly, sensitivity was 47.4% and specificity was 74.7%. Presence of joint surgery may be understood as indicative of more active disease with severe damage.

The inclusion of medication-related variables (Claims + Medications) retained the initial two variables, and ever use of DMARDs and ever use of opioids remained in the model. In comparison to the corresponding continuous model, which retained 12 variables, the binary version only retained only 4 variables. The AUC improved slightly to 0.68 with a sensitivity of 79.2% and specificity of 48.6% at the optimal threshold. Ever use of glucocorticoids was not retained in the final model.

The largest set of candidate variables (Claims + Medications + Laboratory Tests) resulted in a final model with 13 variables, again somewhat smaller than the continuous counterpart with 23 variables. All four variables in the previous model remained. Additionally, testing for viral hepatitis and the total number of DMARDs during the baseline period were included in the final model. From the extended pool of EMR variables, several var-

![Figure 1](Image)

Figure 1. Performance of binary classification models. Cut-off values indicate the thresholds used to dichotomize estimated probabilities of MDA/HDA into binary classifications (MDA/HDA for ≥ cut-off and REM/LDA for < cut-off). Abbreviation: CCR, correct classification rate; Class, model-based classification; HDA, high disease activity; Labs, laboratory test results; LDA, low disease activity; MDA, medium disease activity; Meds, medications; NPV, negative predictive value; PPV, positive predictive value; REM, clinical remission; True, gold standard.
sives were retained. For certain variables such as BP, only the missingness indicator remained, suggesting that the absence/presence status of having BP recorded was informative enough and actual recordings, when present, did not add much. For ESR and CRP values, respective abnormal value indicators were kept in the final model, grouping normal values and missing category together. The AUC was 0.76 with a sensitivity of 83.1% and specificity of 59.6%.

**DISCUSSION**

A model that uses readily available data to estimate RA disease activity would be a valuable addition to epidemiologic population-based studies that lack direct disease activity measures. Prior studies have demonstrated significant challenges in developing and validating these algorithms (2,4). We attempted to build on the prior literature by adding EMR variables that should be available from routine practice and are readily extractable from medical records to claims-based data. We also leveraged novel machine learning strategies to allow the data to drive the choice of variables.

In our models, we found that adding EMR-based information modestly improved model performance metrics. However, we were still unable to estimate disease activity in a meaningful way as a continuous measure. Our model that incorporated EMR data, medication and laboratory data, and claims to classify disease activity as a dichotomized measure did result in a reasonable C-statistic (0.76), indicating the ability to distinguish between moderate/high vs. low disease activity with adequate certainty.

These results indicate that addition of simple EMR-derived variables to claims-derived variables could be useful for improving classification of RA disease activity into high and moderate disease activity vs. low disease activity (correct classification rate = 71.3%) but not for accurately estimating its actual numerical values. Importantly, the continuous estimates or binary classification of RA disease activity measure will not add to confounding control if all the covariates are already included in the outcome analysis or propensity score model. However, it may serve as a summary risk score, which can be easier to handle than individual covariates in settings with a limited sample size. A potentially more useful case of the binary classification is to use it as a stratification variable, for which a correct classification rate of 71.3% may still provide some value. When we are interested in how the effect of a given exposure on the outcome of interest differs by the baseline RA disease activity, stratifying the study cohort by the binary RA disease activity classification may add value beyond what individual covariates can achieve.

We acknowledge several limitations in data and modeling. Ideally, the final model performance should be assessed in a data set completely independent from the entire model building and validation process. However, we did not have a test set because of the small sample size. Although adaptive LASSO is a flexible variable selection strategy, it does not attempt to explore more complex relationships between variables and DAS28-CRP. More advanced supervised machine learning methods, such as deep neural networks (26) and random forest (27), can automatically identify interaction between variables at the cost of being less interpretable and more data-hungry.

Although certain variables included in our final combined model logically correlate with RA disease activity (such as joint surgeries, inflammatory marker elevations, anemia, number and ever use of DMARDs and opioids), our models also incorporated missing EMR data as explanatory variables. For example, presence or absence of EMR recording of systolic BP was deemed more informative than the recorded value itself. Although this is reasonable from a modeling perspective, model interpretability and portability may suffer. The next important step will be determining the degree to which this algorithm may perform in an external cohort with combined EMR-claims data. In such external validation, variables that were important in the BRASS cohort may carry different importance. For example, the tuberculosis screening– and hepatitis screening–related variables contributed to our models. These may have heralded an impending treatment switch or intensification in our local practice and were informative of disease activity. However, this may not generalize to other practice settings. The C-statistic for our Claims + Medications model was only slightly inferior compared to the Claims + Medications + Laboratory Tests model and includes variables that are logically associated with disease activity and are readily accessible in claims (inflammatory markers drawn in the prior year, joint replacement surgery, DMARD use, and opioid use). This may be a reasonable option when the goal is to distinguish moderate/high from low.

In summary, we attempted to improve DAS28-CRP estimation and classification based on claims data by utilizing easily accessible information in the EMR, resulting in a modest improvement for the binary category classification. Numerical estimation of DAS28-CRP was unsatisfactory. External validation of our binary models in a different EMR system is an important future direction. Nonetheless, we believe the present study serves as proof of concept that we can improve our ability to classify RA disease activity in its binary form by supplementing claims data with simple EMR-derived variables.

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AUTHOR CONTRIBUTIONS

Drs. Feldman and Yoshida had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Feldman, Yoshida, Shadick, Weinblatt, Connolly, Alemao, Solomon.

Acquisition of data. Frits, Shadick, Weinblatt.

Analysis and interpretation of data. Feldman, Yoshida, Xu, Alemao, Solomon.

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