ORIGINAL ARTICLE

Clinical Characteristics of Fibromyalgia in a Chronic Pain Population

Mark Gostine, MD*; Fred Davis, MD†; Bradley A. Roberts, MS†; Rebecca Risko, RN†; Michael Asmus, PharmD‡; Joseph C. Cappelleri, PhD§; Alesia Sadosky, PhD‡

Michigan Pain Consultants, Grand Rapids, Michigan; †ProCare Systems Inc., Grand Rapids, Michigan; ‡Pfizer Inc., New York, New York; §Pfizer Inc., Groton, Connecticut, U.S.A.

■ **Abstract**

Objective: To compare fibromyalgia (FM) characteristics among patients identified in a community-based chronic pain cohort based on traditional International Classification of Diagnoses 9th revision (ICD-9) diagnostic coding, with that of patients identified using a novel predictive model.

Methods: This retrospective study used data collected from July 1999 to February 17, 2015, in multiple chronic pain clinics in the United States. Patients were assigned to the FM case group based on specific inclusion criteria using ICD-9 codes or, separately, from results of a novel FM predictive model that was developed using random forest and logistic regression techniques. Propensity scoring (1:1) matched FM patients (cases) to nonmalignant chronic pain patients without FM (controls). Patient-reported measures (eg, pain, fatigue, quality of sleep) and clinical characteristics (ie, comorbidities, procedures, and regions of pain) were outcomes for analysis.

Results: Nine ICD-9 clinical modification diagnoses had odds ratios with large effect sizes (Cohen's $d > 0.8$), demonstrating the magnitude of the difference between the FM and matched non-FM cohorts: chronic pain syndrome, latex allergy, muscle spasm, fasciitis, cervicalgia, thoracic pain, shoulder pain, arthritis, and cervical disorders (all $P < 0.0001$). Six diagnoses were found to have a moderate effect size (Cohen's $0.5 < d > 0.8$): cystitis, cervical degeneration, anxiety, joint pain, lumbago, and cervical radiculitis.

Conclusions: The identification of multiple comorbidities, diagnoses, and musculoskeletal procedures that were significantly associated with FM may facilitate differentiation of FM patients from other conditions characterized by chronic widespread pain. Predictive modeling may enhance identification of FM patients who may otherwise go undiagnosed. ■

Key Words: fibromyalgia, pain, shoulder pain, arthritis, cervical pain, myelitis, myofacial pain syndromes, depression

INTRODUCTION

Fibromyalgia (FM) is a chronic disorder that is characterized by widespread musculoskeletal pain, joint stiffness, and fatigue. FM is typically accompanied by sleep disturbances, depression, and a constellation of other symptoms,[1] and it may also be associated with cognitive difficulties, often referred to as "fibrofog," that affect cognition and memory.[2] Severity of FM can range from mild to incapacitating, resulting in a burden of disease that is not only well-recognized,[3] but also has been shown to increase as severity increases.[4,5]

While functional imaging has enabled visualization of changes in the brain among patients with FM,[6]

Address correspondence and reprint requests to: Bradley Roberts, MS, ProCare Systems Inc., 61 Commerce Ave. SW, Grand Rapids, MI 49503, U.S.A. E-mail: broberts@procaresystems.com.

Disclosures

This study was sponsored by Pfizer. Joseph C. Cappelleri and Alesia Sadosky are employees of Pfizer, the sponsor of this study. Michael Asmus was an employee of Pfizer, the sponsor of this study, during development and submission of this manuscript. Fred Davis, Bradley Roberts, and Rebecca Risko are employees of ProCare Systems, Inc., which received funding from Pfizer for conducting the analyses. Mark Gostine collaborated with Pfizer on this project; he was not financially compensated for his participation or the development of this manuscript. Editorial support was provided by E. Jay Bienen and was funded by Pfizer.

Submitted: October 17, 2016; Revised February 7, 2017; Revision accepted: March 25, 2017

DOI. 10.1111/papr.12583

neither imaging techniques nor laboratory tests are currently available that can be used to clinically identify or confirm an FM diagnosis. Instead, the American College of Rheumatology (ACR) 2010 criteria are used for clinical diagnosis and severity classification of FM.[7] According to these criteria, FM diagnosis is based on 2 scales: one that evaluates the extent of widespread pain Widespread Pain Index (WPI) and the other that evaluates the severity of specific somatic symptoms symptom severity scale (SSS). Two alternative combinations of these scales can be used to indicate an FM diagnosis, either a WPI value of ≥ 7 and SSS value of ≥ 5, or WPI values of 3 to 6 and an SSS value of ≥ 9.[7]

There is no current specific single International Classification of Diagnoses 9th revision, clinical modification (ICD-9-CM) billing code for FM; however, the generally accepted diagnosis code in the medical literature is 729.1. This code is designated as "Myositis and Myalgia, unspecified" and can include other conditions. Thus, when used in clinical or database studies, a diagnosis based strictly on this code may inaccurately reflect the actual number of patients with FM. Additionally, billing is driven by codes associated with procedures performed or symptoms addressed during a discrete encounter, and thus it may go unreported that the patient being treated has FM. Clinical experience also suggests that most community-based physicians do not routinely rely on ACR 2010 criteria, and while there has been widespread adoption of electronic health records (EHRs), these do not include the ACR screening criteria for SSS and WPI. Given the limited amount of time clinicians have to spend during patient visits, there is a need for alternatives that may be more readily available through the EHR to identify patients who may be symptomatic of FM and who may warrant closer examination.

Given the many comorbidities, including other chronic pain conditions, associated with FM and the inconsistent coding, the purpose of this study was to compare 2 methods of examining the clinical characteristics of FM patients in a community-based pain specialty practice compared with those who have chronic pain without FM. While the first method was based on standard and commonly used selection criteria for identifying patients with FM (ie, ICD-9), the second method entailed novel predictive modeling techniques. Such evaluation and comparisons may be of potential benefit for enhancing identification and diagnosis of patients to improve their chances of receiving appropriate treatment.

METHODS

Data Source

The data source for this 2-phase retrospective study was de-identified clinic-level data collected from July 1999 to February 2015, inclusive, in 10 chronic pain clinics in Michigan. All patient data were de-identified and fully compliant with the Health Insurance Portability and Accountability Act; the study protocol was approved by the appropriate institutional review boards. For inclusion in the analysis, chronic pain patients were required to have > 2 touch points, defined as a distinct time for which information could be obtained from the patient (ie, Pain Health Assessment [PHA] questionnaire, office visits, medication prescriptions, and surgeries); completing a PHA was required of all patients.

Phase 1—Traditional Selection Criteria for FM Patients

In phase 1, adult ($\geq$ 18 years) FM patients were identified for inclusion in the case group from among the 82,445 chronic pain patients with > 2 touch points based on the presence of ≥ 2 physician-assigned ICD-9 codes for FM (729.1) separated by at least 1 year, and a length of treatment encompassing at least 1 year. Propensity scoring[8] matched FM cases with controls (nonmalignant chronic pain patients without FM) in a 1:1 ratio based on the potential confounding variables of age, sex, length of treatment, and treating physician specialty (Figure 1A). The means were visually inspected for balance,[9] and standard differences were determined, with an absolute value of $\leq 10\%$ used as a cutoff value for adequate balance, since there is no rule as to how small the standard difference value should be.[8]

Outcomes evaluated included comorbidities, musculoskeletal procedures, and body regions of pain associated with FM. Additionally, items from the PRISM™ PHA (ProCare Systems Inc.)[10] were also used to investigate measures such as functional and psychosocial impairment, pain, fatigue, and quality of sleep. PRISM™ is a patient self-assessment instrument that captures demographic information, and medical and social history. It also collects patient-reported outcomes that include core domains for evaluating treatment efficacy consistent with recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[11]

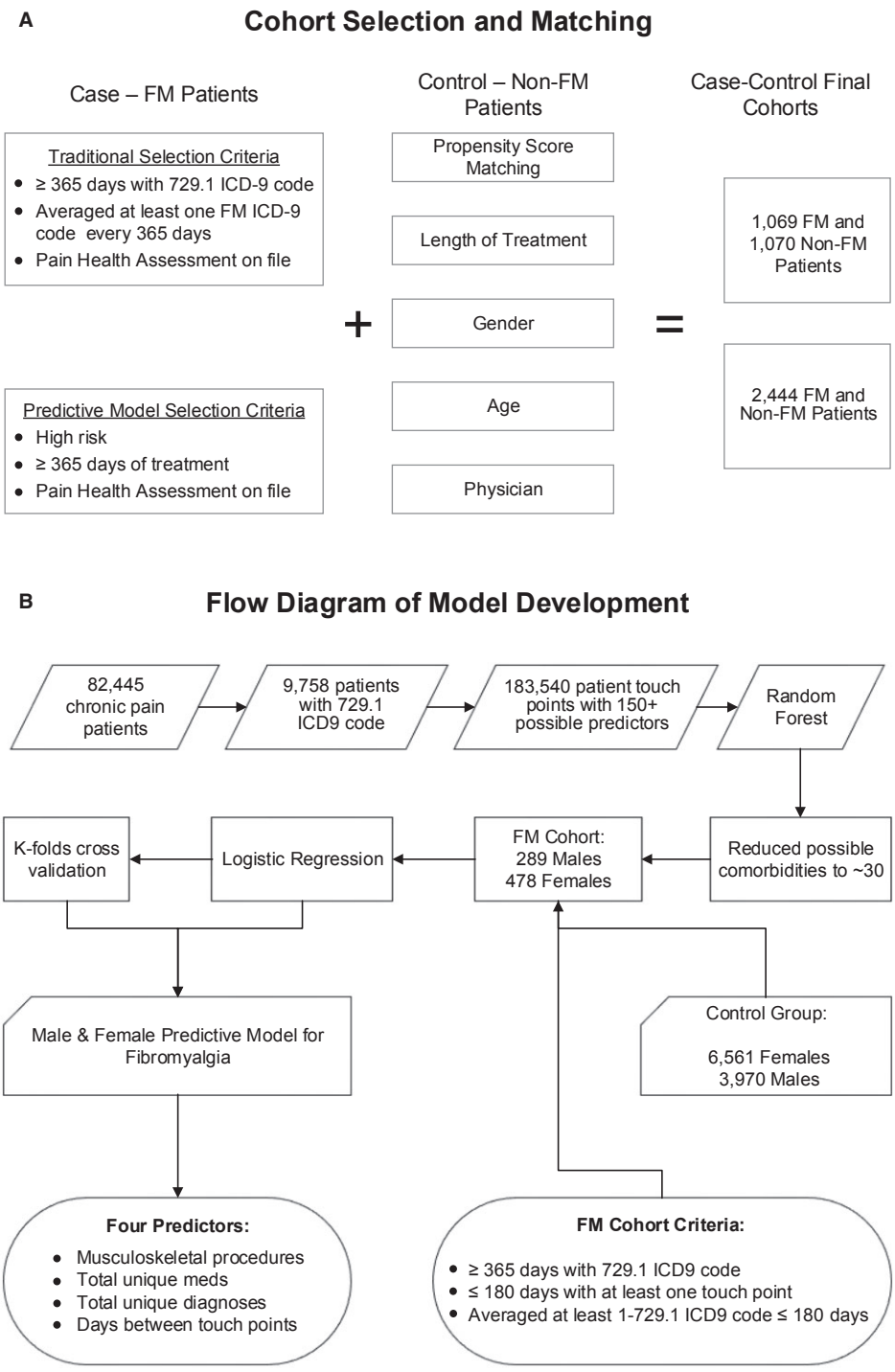

Figure 1. Cohort selection and model development. FM, fibromyalgia.

Phase 2—Predictive Model for Identifying FM Patients

Identification of Potential Variables. In the second phase, FM predictive models were developed separately by gender to identify FM patients. Model development employed several techniques (Figure 1B) applied to the patients with FM who were identified during phase 1. Diagnoses and characteristics relevant to FM that were derived from the medical literature were used to assist in the identification of possible predictive variables.[12–16] The presence of these characteristics were identified

among the FM patients based on 183,540 treatment activity markers, which were defined as any contact with the patient for office visits, injections, therapies, taking a pain health assessment, and writing prescriptions.

Random Forest Model. More than 150 possible predictors were entered into a random forest model as a second step for variable reduction. Random forest modeling is a computationally extensive statistical technique that can accommodate large sets of numerical and categorical variables as input.[17] The model itself consists of ensembles of classification trees that are developed from a series of bootstrapped samples,[18] providing an output that has good predictive performance with respect to diagnostic accuracy for identifying factors associated with the outcome of interest. Built-in cross-validation enables ranking of the importance of the variables associated with the outcome. Random forest has recently been applied to EHR data for predictive modeling of FM and painful diabetic peripheral neuropathy diagnoses.[19]

Logistic Regression. The random forest model identified variables based on their relative importance in partitioning the data into the defined classes from plots of their relative accuracy (Figure 2A) or Gini (Figure 2B); Gini is a measure of the variable's contribution to the overall homogeneity. However, the 30 variables identified from the random forest model for use in the subsequent analyses were derived from the mean decrease in accuracy, since this represents a more robust criterion (ie, averaged over all predictions).

Among the 30 variables, a subsample of FM patients was chosen by applying more stringent criteria to identify the most severe patients requiring more services in a shorter time period. This selection consisted of the following three criteria: (1) at least 365 days of ICD-9 code 729.1, (2) $\leq$ 180 days with at least 1 touch point, and (3) averaged days with at least one ICD-9 code 729.1 $\leq$ 180 days. To establish the control group for model comparison, similar criteria were applied without the assignment of a 729.1 ICD-9 code, but requiring patients to have some type of encounter within the same timeframes. With the cases and controls defined, a logistic regression model was used,[20] and 4 clinically relevant predictors were predefined: musculoskeletal procedures (typically a trigger point injection), total unique medications, total unique diagnoses, and days between touch points. The models were validated by using 10-fold cross-validation, and the resulting models performed well in having high values for area under the receiver operator curve; the female FM predictive model had a value of 0.91, and the male FM predictive model had a value of 0.94. Patients at high risk for FM were then identified by applying the predictive models to the 82,445 chronic pain patients and requiring at least one physician-assigned 729.1 ICD-9 code; high risk was defined as patients ranked in the top ~33% (tertile) odds of having FM. These patients were propensity score matched 1:1 based on gender, age, length of treatment, and physician to identify the comparator control group of patients who had nonmalignant chronic pain but without FM (see Figure 1A).

Statistical Analyses

In both phases, Pearson's chi-square and odds ratios (ORs) were used to assess the significance and magnitude of relationships, with 2-sample *t*-tests used for patient procedures.[21] A mixed model with repeated measures was implemented for patient-reported outcomes.[22] Effect sizes for individual analyses were estimated directly using Cohen's *d* (difference between means divided by the pooled standard deviation) for continuous outcomes[23] or indirectly (log OR multiplied by the square root of 3, divided by π) based on Hasselblad and Hedges for binary outcomes.[24] A standardized effect size of 0.20 standard deviation units is generally considered "small," while 0.50 and 0.80 are "medium or moderate" and "large," respectively.[23,25]

RESULTS

Demographics of the FM Cohorts

In the first phase, 9,758 potential FM patients were identified, from a total of 82,445 chronic pain patients. A total of 1,069 subjects met all inclusion criteria using the traditional selection criteria and were matched to 1,070 controls using the stepwise process of the PSMatching macro, with retention of the extra patient for whom there was no match.[26] The FM population was predominantly female (77.1%), with an average age of 53.5 years and an average length of treatment of 1,793.3 days (Table 1). Standard differences were < 10%, indicating acceptable (see Table 1); prematch standard differences ranged from −27.9% to −45.0% (data not shown).

In the second phase, the predictive modeling identified 2,444 potential patients with a high risk for FM who were propensity score matched with 2,444 nonmalignant chronic pain patients without FM (see Figure 1B). The

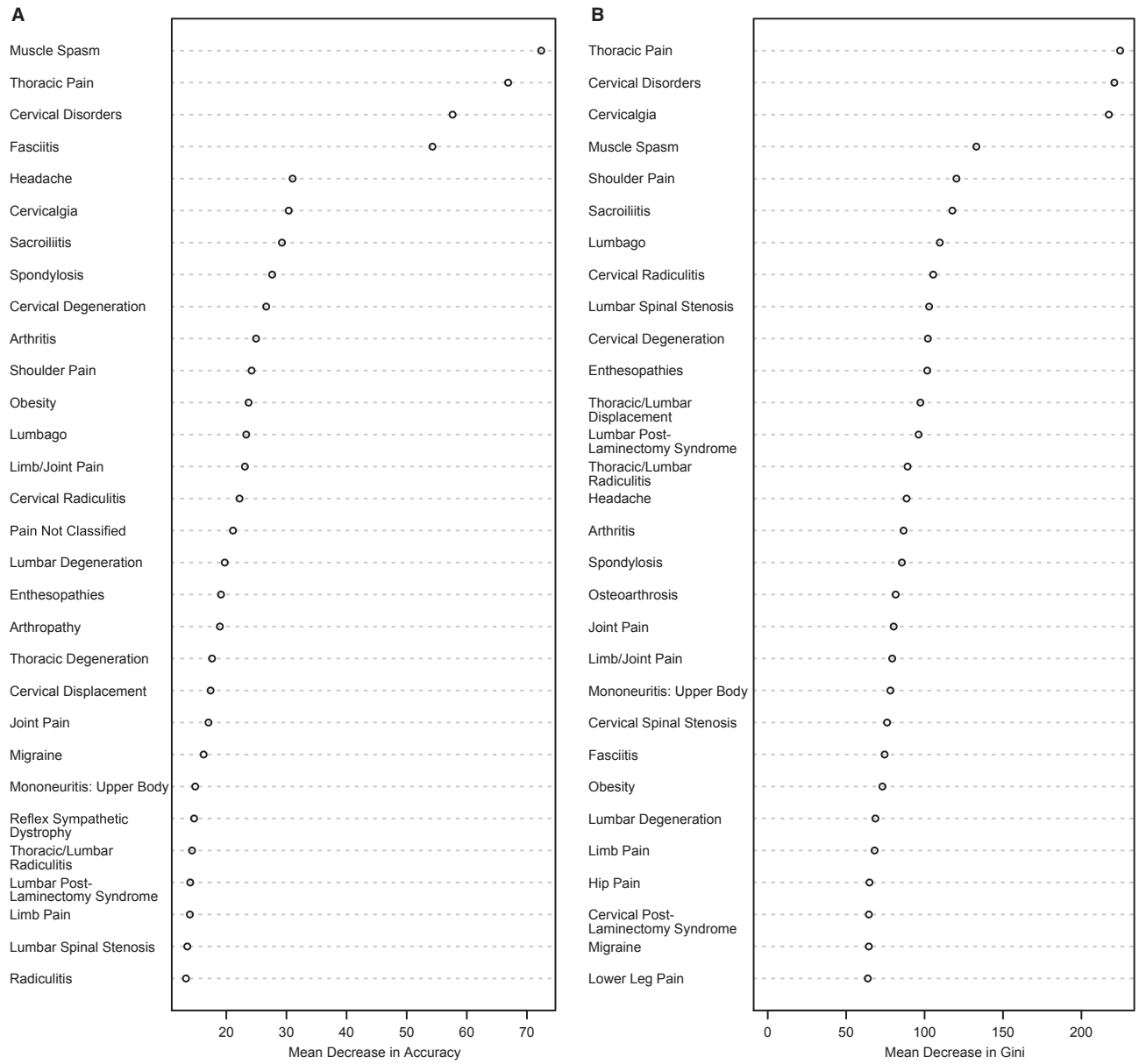

Figure 2. The 30 most important variables identified during random forest modeling as potentially predictive of a diagnosis of fibromyalgia. (A) Based on decrease in accuracy. (B) Based on decrease in Gini score. ICD-9, International Classification of Diagnoses 9th revision.

demographic characteristics of these populations show that age and gender were similar between FM and controls, and comparable to the case-control cohorts. However, duration of treatment was significantly higher ($P = 0.035$) among the control group relative to FM patients identified using the predictive variables (see Table 1).

Characteristics of Conventionally Selected FM Patients

In the traditional selection FM cohort, the average time between touch points was significantly shorter compared with controls, 49 days vs. 140 days ($P < 0.0001$), and overall, FM patients had a 3-fold higher rate of total touch points (ie, visits, prescriptions, PHAs) than non-FM patients. This higher rate among the FM patients relative to matched controls included almost twice as many total prescriptions (15.9 vs. 8.1; $P < 0.0001$) and current procedural terminology–coded procedures, including visits to physical therapy, evaluation and management by midlevel providers and physicians, and injection procedures (178.6 vs. 95.7; $P < 0.0001$; Table 2). FM patients also had more than twice as many individual

Table 1. Demographic Characteristics of the Fibromyalgia and Propensity Score Matched Control Cohorts*

	Phase 1—Traditional Selection				Phase 2—Predictive Model			
Variable	FM case (n = 1,069)	Control (n = 1,070)	Standard Difference (%)	P Value	FM Case (n = 2,444)	Control (n = 2,444)	Standard Difference (%)	P Value
Years of age (mean)	53.5	53.7	−1.9	0.66	55.0	54.9	−0.7	0.81
Male gender (%)	21.9	23.8	−1.6	0.28	23.4	23.2	6.0	0.89
Days of treatment (mean)	1,793.3	1,815.0	−1.6	0.71	2,283.7	2,376.1	−6.0	0.04
Physician	0.014	0.013	1.6	0.74	0.011	0.009	6.0	0.73

*Matching was based on gender, age, length of treatment, and physician. FM, fibromyalgia.

Table 2. Clinical Characteristics Ordered by Effect Size

	Mean (Standard Error)							
	Phase 1—Traditional Selection				Phase 2—Predictive Model			
Variable	FM Case (n = 1,069)	Control (n = 1,070)	P Value	Effect Size	FM Case (n = 2,444)	Control (n = 2,444)	P Value	Effect Size
Total unique diagnoses	14.8 (0.2)	7.6 (0.2)	< 0.0001	1.17	16.7 (0.1)	9.1 (0.1)	< 0.0001	1.20
Total diagnoses	103.2 (2.8)	41.3 (1.4)	< 0.0001	0.87	111.5 (1.8)	53.9 (1.2)	< 0.0001	0.77
Total regions by procedure	3.0 (0.04)	2.2 (0.03)	< 0.0001	0.66	3.3 (0.03)	2.5 (0.02)	< 0.0001	0.70
Total unique musculoskeletal procedures	26.0 (0.4)	18.4 (0.3)	< 0.0001	0.63	29.4 (0.3)	21.5 (0.2)	< 0.0001	0.59
Total musculoskeletal procedures	178.6 (5.4)	95.7 (3.3)	< 0.0001	0.57	210.5 (4.1)	121.1 (2.8)	< 0.0001	0.52
Total unique medications	1.6 (0.1)	0.9 (0.04)	< 0.0001	0.46	1.7 (0.04)	1.0 (0.03)	< 0.0001	0.43
Total prescriptions	15.9 (0.7)	8.1 (0.6)	< 0.0001	0.36	18.8 (0.6)	10.7 (0.4)	< 0.0001	0.33
Total regions by patient-report	3.2 (0.1)	3.0 (0.1)	0.22	0.05	3.3 (0.1)	3.4 (0.1)	0.33	0.03

FM, fibromyalgia.

diagnoses (14.8 vs. 7.6; $P < 0.0001$) and overall total diagnoses (103.2 vs. 41.1; $P < 0.0001$), with large effect sizes of 1.20 and 0.87, respectively (see Table 2).

The 15 diagnoses with the largest effect sizes, demonstrating the magnitude of the difference between the FM and matched cohorts, are shown in Figure 3A. These effect sizes were all at least moderate (ie, $d \geq 0.50$), with the top 9 indicating large effect sizes, as well as ORs showing the odds of an FM diagnosis being 4 to 12 times as likely as those without the diagnoses (see Figure 3A). Chronic pain syndrome was the diagnosis that had both the largest effect size (1.40) and the highest OR (12.8; 95% confidence interval [CI] 3.0 to 54.1), followed by latex allergy, with an effect size of 1.30 and an OR of 10.6 (95% CI 3.8 to 29.8). These ORs can be interpreted as patients with these diagnoses having, respectively, an 11.8- and 9.6-fold greater odds of being diagnosed with FM relative to a patient without these diagnoses.

Characteristics of FM Patients Identified Using the Predictive Model

Similar to the conventional model selection of patients, those patients identified using the predictive model had a significantly shorter average time between touch points of 54 days for FM patients relative to 158 days for matched controls ($P < 0.0001$), and significantly higher rates for each of the variables except for total pain regions (sum of cervical, thoracic, shoulder, arm, knee, hip, chest) affected (see Table 2). Differences were observed among the top 15 comorbidities relative to the populations identified using traditional selection criteria (Figure 3B). In particular, arthropathy, rheumatoid arthritis, thoracic degeneration, and cystitis were among the diagnoses associated with FM in the predictive model population but not among those identified using the traditional criteria. Latex allergy was the diagnosis that had the largest effect size (1.83) and highest OR (27.54, interpreted as patients with latex allergy were approximately 28 times as likely to be diagnosed with FM as patients not diagnosed with a latex allergy).

Overall, FM patients underwent more musculoskeletal procedures in the analysis relative to non-FM patients (Figure 4), with generally similar musculoskeletal procedures reported for the populations identified using traditional and predictive criteria, although some difference were noted. The largest effect sizes were for musculoskeletal procedures using both criteria, which

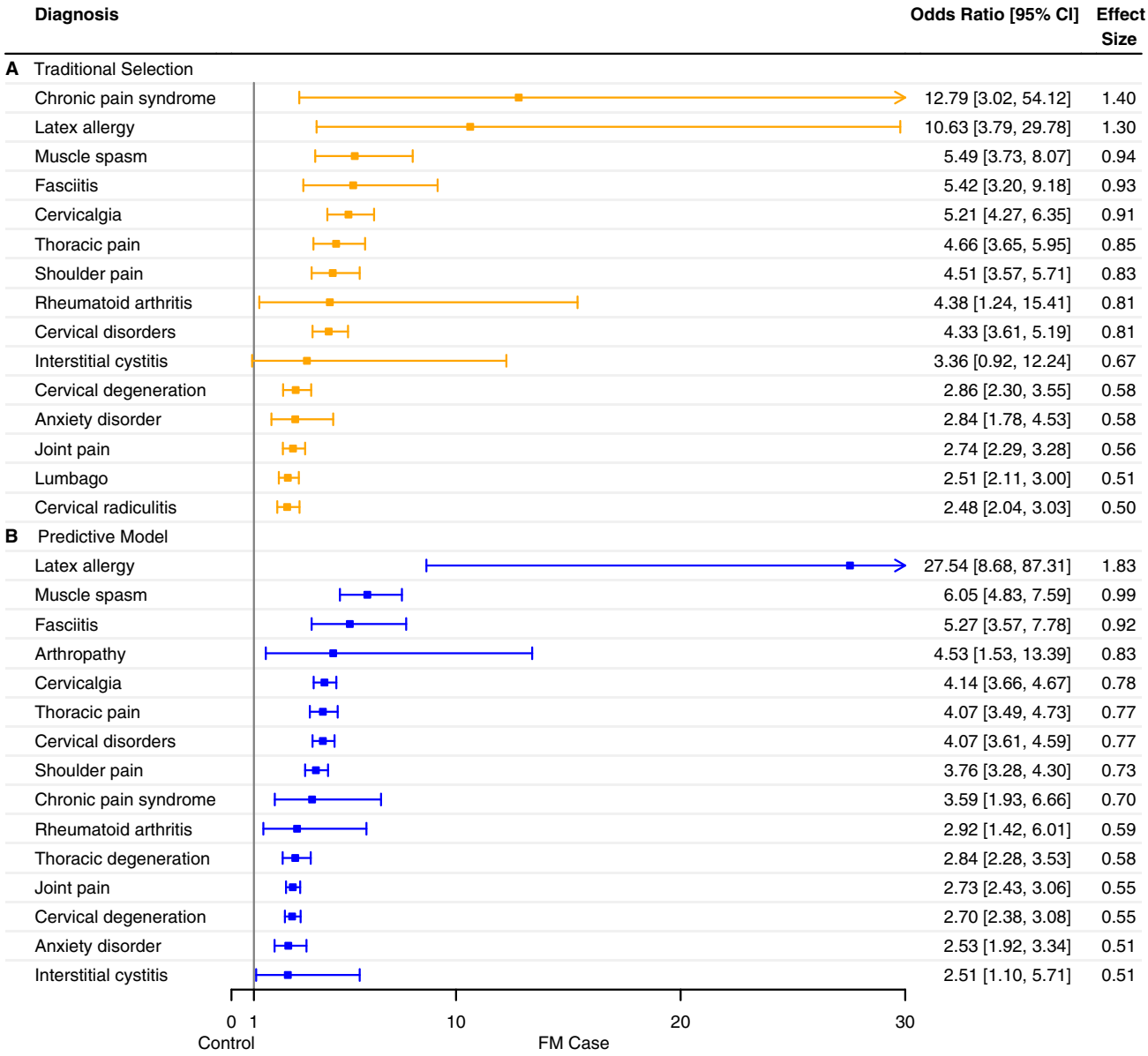

Figure 3. Odds ratios (95% confidence interval [CI]) of the 15 most frequent physician diagnoses in patients with fibromyalgia relative to matched controls without fibromyalgia ranked by magnitude of effect size and odds ratio. (A) Fibromyalgia patients identified using traditional International Classification of Diagnoses 9th revision (ICD-9) criteria. (B) Fibromyalgia patients identified based on a predictive model. Effect size based on Cohen's *d*.

mainly consisted of trigger point injections, and FM patients had nearly 6 more musculoskeletal procedures than non-FM patients during their course of treatment, on average, with trigger point injections accounting for approximately 5 of these procedures.

An examination of the body regions for pain by procedure among patients identified using traditional criteria (Figure 5A) showed significantly higher odds of an FM diagnosis associated with all procedures except hip, with large effect sizes for the shoulder (0.83) and cervical (0.79) regions. Patients with procedures for shoulder pain were 4.49 times as likely to be diagnosed with FM relative to those who did not receive this procedure code, and similarly 4.19 times as likely for those with neck pain–related procedures. Results were generally similar for patients identified using the predictive model (Figure 5B), although the hip also showed a significant difference between FM and controls.

Longitudinal assessment showed that the majority of patients who were assigned 729.1 ICD-9 codes or for

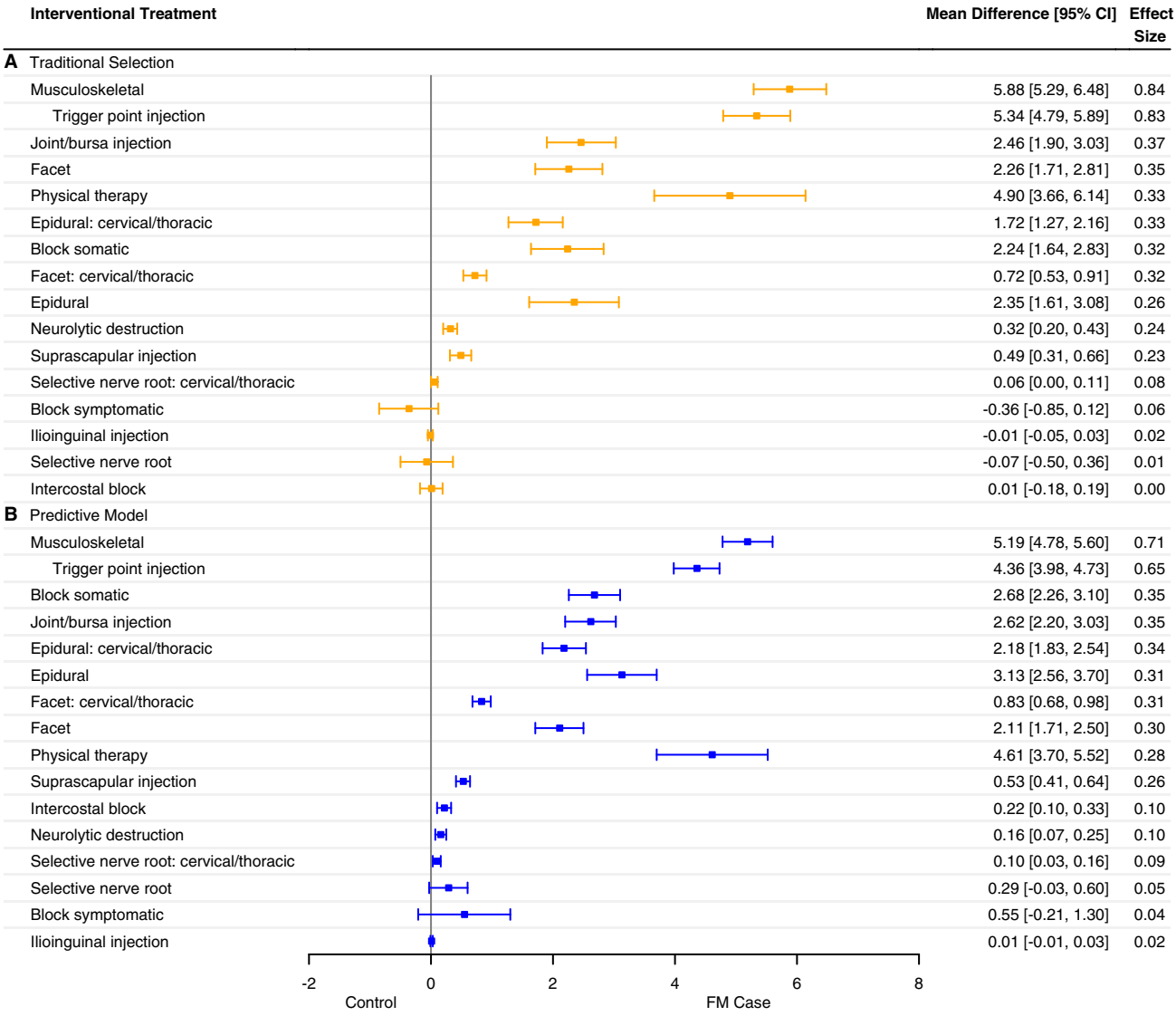

Figure 4. Mean difference (95% confidence interval [CI]) in average number of interventional treatments in patients with fibromyalgia relative to matched controls ranked by magnitude of effect size. (A) Fibromyalgia patients identified using traditional International Classification of Diagnoses 9th revision (ICD-9) criteria. (B) Fibromyalgia patients identified based on a predictive model. Effect size estimated using Cohen's *d*.[23]

whom the corresponding approach of musculoskeletal procedures was used had these assignments during the first 1 to 2 years regardless of the selection criteria used (Figure 6); musculoskeletal procedures generally matched the ICD-9. Similar longitudinal patterns were observed for total unique medications and total unique diagnoses (data not shown).

Evaluation of patient-reported outcomes from the PHA showed that the differences between FM and non-FM patients were small and resulted in negligible effect sizes (ie, < 0.01) (data not shown).

DISCUSSION

Diagnosis and coding of FM remains a challenge. This predictive modeling study identified 4 predictive variables (musculoskeletal procedures, typically a trigger point injection; total unique medications; total unique diagnoses; and days between touch points) that can be used to help clinicians differentiate FM patients from other chronic painful conditions. Results from the 2 approaches (ie, traditional ICD-9 coding vs. use of predictive modeling) for identifying FM patients were generally similar with regard to characteristics

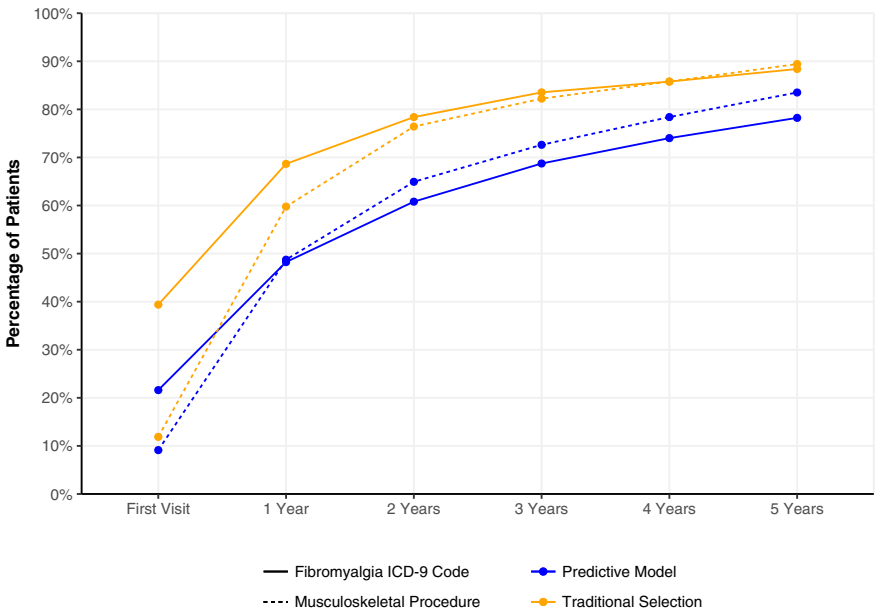

Figure 5. Longitudinal assessment of fibromyalgia International Classification of Diagnoses 9th revision (ICD-9) code and musculoskeletal procedures during their first clinical visit or in their following years of treatment

associated with FM. However, predictive modeling resulted in a larger sample of FM patients, suggesting that use of predictive variables enhanced our ability to identify patients at higher risk for FM.

Our predictive modeling results showed that disease burden is greater among FM patients relative to matched predictive modeling controls. This is consistent with the cohorts identified using traditional selection criteria, as

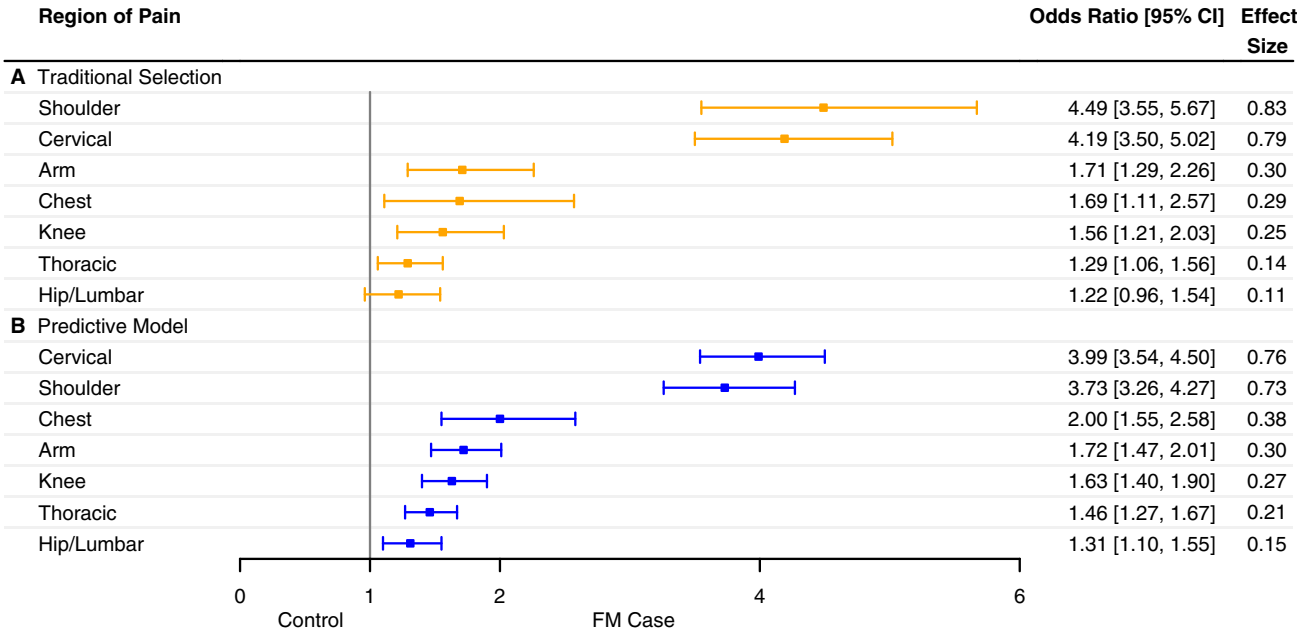

Figure 6. Regions of pain by procedure, using Current Procedural Terminology code, ranked by magnitude of effect size and odds ratio. (A) Fibromyalgia (FM) patients identified using traditional ICD-9 criteria. (B) Fibromyalgia patients identified based on a predictive model. Effect size based on Hasselblad and Hedges.[24] CI, confidence interval.

well as with other studies that also reported a high comorbidity burden among FM patients.[27–29] Importantly, these results quantified the burden and showed, using 2 different methods for selecting FM patients, that regardless of the selection method, FM patients had almost twice as many diagnoses as controls, enabling identification of specific conditions that were associated with a greater likelihood of receiving an FM diagnosis, including the presence of latex allergy. There was general concordance in the top diagnoses between the 2 methods of identifying patients, suggesting that common comorbid conditions may be appropriate for identifying patients who may require additional evaluation for FM. However, the overall prevalence of comorbidities was higher among patients identified using the predictive model, suggesting that this method selects patients who may be at a higher risk for comorbidities, as well as having a more diverse symptomology than patients selected by traditional methods.

Interestingly, this is the first report in the medical literature suggesting a significant association between latex allergy and an FM diagnosis; patients with a latex allergy had greater than 9-fold and 26-fold higher odds of being diagnosed with FM relative to those who did not have such an allergy among the traditional criteria and predictive modeling groups, respectively. This apparent relationship between latex allergy and FM may be representative of an increased skin sensitivity response, which is not unusual in sufferers with the condition, and may be an indicator of multiple chemical sensitivity disorder, which is characterized by persistent symptoms temporally related to exposure of chemically unrelated compounds at doses below those that cause harmful effects.[30,31] While it can be proposed that multiple chemical sensitivity disorder may potentially coexist in FM patients, contributing to sensitization and widespread chronic pain, the presence of latex allergy itself may also represent a signal indicating the need for further clinical evaluation of patients for FM. This relationship between latex allergy and FM, and the implications for broader environmentally related sensitivity, warrant further investigation.

The significantly higher rates of musculoskeletal procedures among the FM patients relative to controls regardless of the selection criteria, combined with the shorter time between touch points, is a clear demonstration of the healthcare-seeking behavior and greater resource use that has consistently been reported among FM patients.[32–34] This greater resource use is consistent with a previous analysis that identified 8 of the 10 most important variables predictive of an FM diagnosis as healthcare resource utilization variables.[35] It should be noted that among the musculoskeletal procedures in the current analysis, patients with FM had on average 5 more trigger point injections than controls, despite limited evidence for the efficacy of such procedures in FM.[36,37] The results also showed there was a significant association between FM patients and the body region where they received the musculoskeletal procedures. The shoulder and cervical regions were the most frequent sites for procedures, with FM patients identified using both traditional and modeling criteria nearly 4 times as likely to be treated in these regions as non-FM patients.

There were no significant differences between FM and matched cohorts for any of the patient-reported items from the PHA, suggesting the difficulty in identifying FM patients using patient-reported criteria. While specific clinical variables appear to represent the primary differences between these populations, it is also possible that the PHA items may not adequately reflect or capture key variables that are reported by FM patients.

The clinical relevance of this study is that it proposes 4 predictive variables based on information that is likely to be readily accessible, with information on 3 of these variables (musculoskeletal procedures, total unique medications, and total unique diagnoses) available even at an initial visit with a new patient and certainly within the first year. This availability early in the follow-up, as indicated by the longitudinal assessment results, is consistent with the recognized pattern of healthcare-seeking behavior among FM patients prior to receiving a diagnosis, which is often delayed.[16] For the identified variables, in particular, it would be possible for physicians to determine the medications, diagnoses, and procedures that have been assigned to a patient over a 12-month period, with a high relative score in a patient with somatic complaints or frequent visits indicating patients who may be symptomatic of FM. However, these results also suggest the appropriateness of developing an algorithm, using these variables, for incorporation into EHR that could prompt, via computer notification, a physician to consider an FM diagnosis.

STRENGTHS AND LIMITATIONS

Strengths of this study include a large study size, enabling high statistical power and the ability to detect effects and determine their size, and the use of matching

to controlling for confounding variables. Additionally, the predictive model considered the presence of physician-assigned FM ICD-9 codes as less stringent, increasing the number of true FM patients to be included in the analysis, although this reduction in stringency may also be considered a limitation in that it may have incorporated a modeling error for identifying FM patients. In this regard, it is important to note that the variables used in the predictive model were highly predictive of FM patients in our chronic pain practices, and that the reduced stringency was needed because ICD-9 codes are infrequently used, especially in our practice. Consequently, generalizability may be limited outside of our practice until more complex predictive modeling can confirm the external validity.

Other limitations of this study include that databases such as those used here may be subject to errors in coding or misclassification. In this regard and as previously mentioned, FM is inconsistently coded because there is no ICD-9 code specific to FM, and thus it is possible that some of the patients included in the matched cohort did have FM. This limitation may be especially relevant, since diagnostic criteria for diagnosing FM were absent and identification was dependent on physician-assigned ICD-9 codes, which are driven by procedure and may not be consistent or carried through to additional visits. Additionally, evaluation of healthcare resource categories was limited, including an absence of outpatient visits. Lastly, inclusion of length of treatment in the matching algorithm could be potentially criticized, since the time from disease onset to treatment initiation may be different between cohorts, potentially affecting the predictive value of the proposed variables. However, it should be noted that not only was matching performed subsequent to predictive model selection, but that patients often delay seeking treatment, and thus neither disease onset nor specific treatment initiation can adequately be captured. Furthermore, matching on length of treatment would minimize potential variation between cohorts based on administrative codes over various times of treatment, enabling comparison of FM and non-FM patients regardless of time, thus enhancing discriminatory power.

Thus, based on these limitations, results should be considered as hypothesis generating and warrant further investigation. Nevertheless, from a statistical perspective, the results suggest that the methods described here represent a powerful approach for use in case-control studies that have designs and goals similar to the current one with the caveat that it is also necessary to understand the control population based on the complexities of a chronic disease such as FM. This understanding of both case and control populations may help determine why the FM cohort identified using the predictive modeling had differences not inherently related to the disease but rather compared with the comparison group.

CONCLUSIONS

Multiple comorbidities, diagnoses, and musculoskeletal procedures were associated with a diagnosis of FM in this study. While the number and types of these variables were generally similar between the FM populations identified using traditional ICD-9 criteria and the predictive model, the predictive model allowed a broader selection of FM patients and, by doing so, may assist in more accurately identifying patients who may otherwise go undiagnosed, enabling early and appropriate treatment. The data from this study may enhance development of a clinical decision support system that can be incorporated into algorithms for use in EHRs and other programs to better identify and treat FM patients.

CONFLICT OF INTERESTS

The authors declared no potential conflict of interests, with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Bennett RM. Clinical manifestations and diagnosis of fibromyalgia. *Rheum Dis Clin North Am*. 2009;35:215–232.

2. Kravitz HM, Katz RS. Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. *Rheumatol Int*. 2015;35:1115–1125.

3. Annemans L, Le Lay K, Taieb C. Societal and patient burden of fibromyalgia syndrome. *Pharmacoeconomics*. 2009;27:547–559.

4. Schaefer C, Chandran A, Hufstader M, et al. The comparative burden of mild, moderate and severe fibromyalgia: results from a cross-sectional survey in the United States. *Health Qual Life Outcomes*. 2011;9:71.

5. Chandran A, Schaefer C, Ryan K, Baik R, McNett M, Zlateva G. The comparative economic burden of mild, moderate, and severe fibromyalgia: results from a retrospective chart review and a cross-sectional survey of working-age U.S. adults. *J Manag Care Pharm*. 2012;18:415–426.

6. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic

review on structural and functional brain MRI. *Semin Arthritis Rheum*. 2014;44:68–75.

7. Wolfe F, Clauw DJ, Fitzcharles M-A, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res*. 2010;62:600–610.

8. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.

9. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.

10. Juckett DA, Davis FN, Gostine M, Reed P, Risko R. Patient-reported outcomes in a large community-based pain medicine practice: evaluation for use in phenotype modeling. *BMC Med Inform Decis Mak*. 2015;15:41.

11. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.

12. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain*. 2009;10:777–791.

13. Buskila D. Developments in the scientific and clinical understanding of fibromyalgia. *Arthritis Res Ther*. 2009;11:242.

14. Kindler LL, Bennett RM, Jones KD. Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Manag Nurs*. 2011;12:15–24.

15. Silverman S, Sadosky A, Evans C, Yeh Y, Alvir J, Zlateva G. Toward characterization and definition of fibromyalgia severity. *BMC Musculoskelet Disord*. 2010;11:66.

16. Choy E, Perrot S, Leon T, et al. A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC Health Serv Res*. 2010;10:102.

17. Breiman L. Random forests. *Mach Learn*. 2001;45:5–32.

18. Kuhn M, Johnson K. *Applied Predictive Modeling*. New York, NY: Springer; 2013.

19. Emir B, Mardekian J, Masters ET, Clair A, Kuhn M, Silverman S. Predictive modeling of a fibromyalgia diagnosis: increasing the accuracy using real world data [abstract]. *Arthritis Rheumatol*. 2014;66(suppl):S910.

20. Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2013.

21. Rosner B. *Fundamentals of Biostatistics*. 8th ed. Boston: Brooks Cole; 2015.

22. Fitzmaurice G, Laird N, Ware J. *Applied Longitudinal Analysis*. New York, NY: John Wiley & Sons; 2004.

23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

24. Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. *Psychol Bull*. 1995;117:167–178.

25. Cappelleri JC, Zou KH, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T. *Patient-Reported Outcomes: Measurement, Implementation and Interpretation*. Boca Raton, FL: Chapman & Hall/CRC Press; 2013.

26. Coca-Perraillon M. *Local and global optimal propensity score matching*. Paper 185-2007, SAS Global Forum 2007. http://www2.sas.com/proceedings/forum2007/185-2007.pdf (accessed June 8, 2016)

27. Lachaine J, Beauchemin C, Landry PA. Clinical and economic characteristics of patients with fibromyalgia syndrome. *Clin J Pain*. 2010;26:284–290.

28. Gore M, Tai K-S, Chandran A, Zlateva G, Leslie D. Clinical comorbidities, treatment patterns, and healthcare costs among patients with fibromyalgia newly prescribed pregabalin or duloxetine in usual care. *J Med Econ*. 2012;15:19–31.

29. Knight T, Schaefer C, Chandran A, Zlateva G, Winkelmann A, Perrot S. Health-resource use and costs associated with fibromyalgia in France, Germany, and the United States. *Clinicoecon Outcomes Res*. 2013;5:171–180.

30. Spencer TR, Schur PM. The challenge of multiple chemical sensitivity. *J Environ Health*. 2008;70:24–27.

31. Dantoft TM, Andersson L, Nordin S, Skovbjerg S. Chemical intolerance. *Curr Rheumatol Rev*. 2015;11:167–184.

32. White LA, Robinson RL, Yu AP, et al. Comparison of health care use and costs in newly diagnosed and established patients with fibromyalgia. *J Pain*. 2009;10:976–983.

33. Masters ET, Mardekian J, Emir B, Clair A, Kuhn M, Silverman S. Electronic medical record data to identify variables associated with a fibromyalgia diagnosis: importance of healthcare resource utilization. *J Pain Res*. 2015;8:131–138.

34. Schaefer C, Mann R, Masters ET, et al. The comparative burden of chronic widespread pain and fibromyalgia in the United States. *Pain Pract*. 2016;16:565–579.

35. Emir B, Makinson G, Seitzman R, Whiteley J. The burden of atopic dermatitis in adults: results from the National Health and Wellness Survey. *Curr Med Res Opin*. 2016;32:1645–1651.

36. Hong CZ, Hsueh TC. Difference in pain relief after trigger point injections in myofascial pain patients with and without fibromyalgia. *Arch Phys Med Rehabil*. 1996;77:1161–1166.

37. Affaitati G, Costantini R, Fabrizio A, Lapenna D, Tafuri E, Giamberardino MA. Effects of treatment of peripheral pain generators in fibromyalgia patients. *Eur J Pain*. 2011;15:61–69.