ABSTRACT

Objective Patients and physicians commonly differ in their assessments of rheumatoid arthritis (RA) activity. Clinically meaningful discordance thresholds or validation of their ability to predict functional outcomes are lacking. We explored whether an unbiased, person-centred latent profile analysis (LPA) approach could classify cases based on patient global assessment (PtGA) and physician global assessment (MDGA) assessments of RA activity. We further examined whether the LPA groups displayed greater differences in clinical outcomes compared with traditional threshold-based groups. Finally, we evaluated whether LPA yielded higher explanatory power for clinical outcomes.

Methods LPA was performed in 618 patients with established RA from a single centre. A threshold-based discordance definition was used as a comparator, with patients classified into concordant (PtGA–MDGA within ±3 cm), positively discordant (PtGA–MDGA ≥3 cm) and negatively discordant groups (PtGA–MDGA ≤−3 cm).

Results LPA yielded five distinct groups: low PtGA/low MDGA (35.9%), moderate PtGA/moderate MDGA (18.6%), high PtGA/high MDGA (14.7%), high PtGA/low MDGA (23.3%) and low PtGA/high MDGA (7.4%). Groups differed across clinical, physical function, pain, fatigue, health-related quality of life, work productivity and activity impairment outcomes (p<0.001). Concordance groups, in particular, displayed marked heterogeneity in outcomes depending on the magnitude of disease activity reported, with the low/low group faring the best (p<0.001). The LPA solution demonstrated superior explanatory power for all outcomes (p<0.001).

Conclusions We confirmed the validity and advantages of LPA in characterising the relationship between PtGA and MDGA over a conventional threshold-based definition. LPA yielded optimally distinct, clinically meaningful and cohesive groupings, demonstrating superior explanatory power for disease-related outcomes of interest.

INTRODUCTION

Patients and physicians commonly differ in their evaluations of rheumatoid arthritis (RA) activity.1–4 Such discrepancies have been traditionally reported as a difference or discordance score by subtracting physician global assessment (MDGA) from patient global assessment (PtGA).1 2 4 5 Based on this, patients are arbitrarily classified as concordant, positively discordant (higher patient activity) or negatively discordant (higher physician activity). Despite this being intuitively appealing and computationally convenient, there are neither empirical evidence nor strong a priori hypotheses supporting the number or nature of the groups that qualify the relationship between PtGA and MDGA. Both are integral components of the American College of Rheumatology.
Rheumatology (ACR) core set and (some) remission definitions and further inform therapeutic decisions.\(^6\)\(^7\) Since determinants of those scores and their relative contributions are vastly disparate, the concept of a discrepancy score generated by simple subtraction of two heterogeneous constructs as a predictor of functional outcomes is theoretically and statistically problematic.\(^8\) Moreover, the ability of the various, widely reported arbitrary cut-offs to optimally differentiate clinical, functional and health-related quality of life (HRQoL) outcomes between patient groups has not been explored. Additionally, the magnitude of RA activity patients and physicians consensually report is not taken into consideration in the conventional framework of a difference score. It has been shown that when RA is in remission, patients enjoy superior physical function and incur less radiographic progression than when it is highly active.\(^9\)

Another concern is that studies evaluating the impact of patient–physician discordance on various outcomes of interest have used variable-centred methodologies such as multiple regression;\(^1\)\(^4\); such approaches assume that the entire population is homogeneous and therefore results reflect the relationships averaged over the entire population. Additionally, since they focus on the structure of the variables across persons, rather than the patterns of response within persons,\(^10\) they may be inappropriate when seeking to interpret individual data.\(^11\) In contrast, person-centred approaches assume that the population is heterogeneous and allow for examination of patterns and relationships among variables at the individual level.\(^11\)\(^15\)

Latent profile analysis (LPA) is an empirically derived, person-centred approach that focuses on relationships among individuals with the purpose of sorting them into groups of subjects who are similar to each other and different from the other groups. It identifies the smallest number of latent groups required to account for the distribution of individuals across indicators.\(^14\)\(^15\) The number of groups that best fits the data is determined statistically rather than subjectively.\(^16\) The purpose of our study was to evaluate the ability of LPA to classify cases based on the patterns of relationships between PtGA and MDGA. We then examined the potential overlap and discrepancies between the latent profiles and traditional discordance groups and compared their respective explanatory power for outcomes of interest. We lastly assessed the concurrent validity of the LPA-generated groups by exploring associations between the profiles and clinical, functional and HRQoL outcomes.

**METHODS**

**Study design and participants**

Study participants were enrolled in the Harbor-University of California Los Angeles (UCLA) prospective observational RA cohort between 2012 and 2017.\(^17\) The first visit with complete data available for all predictors and outcomes of interest within that time frame was selected for analysis. We evaluated 618 patients with established RA. Patients were included in the study if they were ≥18 years old and fulfilled 2010 ACR criteria for RA.\(^18\) Patients with overlapping autoimmune syndromes or comorbid conditions that could confound RA treatments (including chronic infections, advanced or decompensated heart failure, class II chronic kidney disease or above and cancer within 5 years) or at risk of suicide were excluded. All patients provided written informed consent in compliance with the Helsinki Declaration, and the study was approved by the Harbor-UCLA Institutional Review Board.

**Measures**

PtGA and MDGA ratings were recorded on 10 cm visual analogue scale (VAS) anchored by ‘very good’ or ‘no activity’ on the left and ‘very bad’ or ‘high activity’ on the right, respectively. Prior to the visit, patients completed self-report questionnaires; the PtGA question asked was ‘Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?’. This was in accordance to the proposed phrasing by the ACR/European Leagues Against Rheumatology remission criteria related to disease activity.\(^19\)\(^20\) After conclusion of the index visit, the examining physician (blinded to the patient’s rating) recorded their activity evaluation (MDGA) based on history, physical examination and available laboratory tests. The prompt given to the physician was ‘Mark on the line below to indicate disease activity (independent of the patient’s self-assessment)’. The conventional discordance definition comparator included a PtGA–MDGA difference score of ≥3, informed by a recent meta-analysis indicating this to be the most frequently used threshold (5); based on this cut-off, patients were classified into three groups: concordant (PtGA–MDGA within ±3 cm), positively discordant (PtGA–MDGA ≥3 cm) and negatively discordant (PtGA–MDGA ≤−3 cm).

Demographic, clinical, serological, laboratory, radiographic and treatment data were obtained via chart review. Disease activity assessment was based on 28-joint counts for tenderness joint count, swelling joint count and erythrocyte sedimentation rate (ESR). Presence of erosions and irreversible articular damage (IAD) defined as subluxation, fusion, contracture or fixed deformity, arthrodesis or prosthesis were recorded. The presence of fibromyalgia based on the ACR preliminary classification criteria\(^21\) was also captured.

Physical function was evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI).\(^22\) The nine-item Patient Health Questionnaire (PHQ-9)\(^23\)\(^24\) assessed depressive symptoms (range 0–27). Pain and fatigue were both measured using 10 cm VAS. HRQoL was evaluated by the physical component summary and mental component summary and eight domain scores of the 36-item Short Form Survey (SF-36).\(^25\) The Work Productivity and Activity Impairment Questionnaire\(^26\) assessed activity impairment due to RA and percentage of work productivity loss among employed subjects.
**Statistical analysis**

We performed LPA using the Mplus software package (Muthen & Muthen). LPA models with increasing number of groups were fit to the data. The optimal number of profiles was determined based on the Bayesian information criterion, the Vuong-Lo-Mendell-Rubin likelihood ratio test, the Akaike information criterion and entropy. An a priori decision was made to abort testing models with increasing group numbers if at least two fit statistics suggested no further improvement. The Mplus output includes scores for the conditional probability of each patient being a member of any of the LPA groups, allowing evaluation of how well the model classifies patients. For the purposes of group comparison and external validation, we assigned patients to the profile for which they had the highest conditional probability. Latent profiles were related to demographic and clinical characteristics with analysis of variance (ANOVA) or $\chi^2$ tests. The meaningfulness of the LPA solution was assessed using analysis of covariance, which evaluated between-group differences on clinical, functional and HRQoL outcomes. We used adjusted $\Delta R^2$ value (per cent unique variance explained) to assess the incremental explanatory power of regression models from the LPA-derived solution compared with the traditional discordance group definition to predict outcomes of interest after the effects of relevant clinical covariates had been removed. Age, gender, RA duration, IAD and fibromyalgia were included as descriptive clinical variables in all covariate adjusted analyses. Significance level was set at $p<0.05$, and post hoc pairwise comparisons were Benjamini-Hochberg corrected. Analyses were performed using SPSS V.21.

**RESULTS**

**LPA identifies five distinct patient groups**

A five-group solution provided the best fit for the data (online supplementary table 1). The five distinct patient groups based on different pairings of PtGA and MDGA appear in figure 1: group 1: low PtGA/low MDGA (n=222, 35.9%); group 2: moderate PtGA/moderate MDGA (n=115, 18.6%); group 3: high PtGA/high MDGA (n=91, 14.7%); group 4: high PtGA/low MDGA (n=144, 23.3%); and group 5: low PtGA/high MDGA (n=46, 7.4%). Demographics and clinical characteristics for all groups are summarised in table 1 below.

Patients were largely female with established, robustly seropositive and erosive RA. Seropositivity, radiographic erosions and treatment characteristics were similarly distributed across all LPA groups. Group 4 members were older, with longer disease duration and higher fibromyalgia rates compared with other groups (all $p\leq0.01$). Clinical and serological inflammatory burden was significantly different across groups ($p<0.001$).

**Comparisons of LPA and traditional discordance groups**

The PtGA and MDGA distributions across the three traditional threshold-based groups (negatively discordant, concordant and positively discordant versus those in the LPA-generated class definition) are shown in online supplementary figure 1. Similar to the traditional concordance category, patients in LPA groups 1, 2 and 3 displayed congruent PtGA and MDGA scores; however, this congruence referred to three very different inflammatory activity states. In group 1, both parties reported low disease activity (mean PtGA and MDGA of 1.9 and
Table 1  Demographic and clinical characteristics for latent profile groups

<table>
<thead>
<tr>
<th>Latent profiles</th>
<th>Moderate PtGA/low MDGA (n=222)</th>
<th>Low PtGA/low MDGA (n=115)</th>
<th>High PtGA/high MDGA (n=91)</th>
<th>Low PtGA/high MDGA (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.4±12.1a, 50.8±10.9a</td>
<td>49.9±11.0a, 55.4±11.1a</td>
<td>49.8±10.9a, 9.1±9.1a</td>
<td>49.8±10.9a, 9.1±9.1a</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>186 (83.8), 99 (86.1)</td>
<td>82 (90.1), 131 (91.0)</td>
<td>39 (84.8), 39 (84.8)</td>
<td>39 (84.8), 39 (84.8)</td>
</tr>
<tr>
<td>RA duration, years</td>
<td>10.5±7.9a, 10.2±7.6b</td>
<td>9.2±7.3a, 12.8±9.8b</td>
<td>9.1±9.1a, 9.1±9.1a</td>
<td>9.1±9.1a, 9.1±9.1a</td>
</tr>
<tr>
<td>RF positive</td>
<td>207 (93.2), 106 (92.2)</td>
<td>106 (92.2), 128 (88.9)</td>
<td>42 (91.3), 42 (91.3)</td>
<td>42 (91.3), 42 (91.3)</td>
</tr>
<tr>
<td>ACPA positive</td>
<td>197 (88.7), 101 (87.8)</td>
<td>81 (89.0), 124 (86.1)</td>
<td>42 (91.3), 42 (91.3)</td>
<td>42 (91.3), 42 (91.3)</td>
</tr>
<tr>
<td>Erosions</td>
<td>110 (49.5), 44 (37.4)</td>
<td>44 (37.4), 84 (37.4)</td>
<td>24 (52.2), 24 (52.2)</td>
<td>24 (52.2), 24 (52.2)</td>
</tr>
<tr>
<td>IAD present</td>
<td>53 (23.9), 16 (13.9)</td>
<td>16 (13.9), 36 (25.0)</td>
<td>5 (10.9), 5 (10.9)</td>
<td>5 (10.9), 5 (10.9)</td>
</tr>
<tr>
<td>Number of csDMARDs</td>
<td>1.6±0.9, 1.4±0.9</td>
<td>1.3±1.1, 1.5±1.0</td>
<td>1.6±1.0, 1.6±1.0</td>
<td>1.6±1.0, 1.6±1.0</td>
</tr>
<tr>
<td>bDMARD use</td>
<td>74 (33.3), 33 (36.3)</td>
<td>33 (36.3), 50 (43.7)</td>
<td>15 (32.6), 15 (32.6)</td>
<td>15 (32.6), 15 (32.6)</td>
</tr>
<tr>
<td>SJC (28)</td>
<td>1.1±1.5a, 10.5±4.7c</td>
<td>1.0±1.3, 9.9±4.2a</td>
<td>9.9±6.2, 9.9±6.2a</td>
<td>9.9±6.2, 9.9±6.2a</td>
</tr>
<tr>
<td>TJC (28)</td>
<td>1.2±2.5a, 12.9±6.5c</td>
<td>2.0±3.7, 9.9±6.2a</td>
<td>9.9±6.2, 9.9±6.2a</td>
<td>9.9±6.2, 9.9±6.2a</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>28.0±17.2a, 52.2±26.1c</td>
<td>31.1±19.2a, 42.7±21.7b</td>
<td>42.7±21.7b, 42.7±21.7b</td>
<td>42.7±21.7b, 42.7±21.7b</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.6±0.7c, 2.6±3.2c</td>
<td>2.6±3.2, 1.7±2.9c</td>
<td>1.7±2.9, 1.7±2.9c</td>
<td>1.7±2.9, 1.7±2.9c</td>
</tr>
<tr>
<td>DAS28-ESR</td>
<td>3.0±0.9c, 5.0±0.7c</td>
<td>6.5±0.8c, 3.9±0.9c</td>
<td>5.4±0.8, 5.4±0.8</td>
<td>5.4±0.8, 5.4±0.8</td>
</tr>
<tr>
<td>PtGA</td>
<td>1.9±1.3c, 7.4±1.5c</td>
<td>6.9±1.6, 2.3±1.5c</td>
<td>2.3±1.5, 2.3±1.5c</td>
<td>2.3±1.5, 2.3±1.5c</td>
</tr>
<tr>
<td>MDGA</td>
<td>1.0±1.0d, 8.6±1.2</td>
<td>1.2±1.1, 8.1±1.4</td>
<td>8.1±1.4, 8.1±1.4</td>
<td>8.1±1.4, 8.1±1.4</td>
</tr>
<tr>
<td>PtGA–MDGA difference</td>
<td>0.8±1.5c, 0.8±1.7d</td>
<td>−1.2±1.7d, 5.7±1.5c</td>
<td>−5.8±1.6d, −5.8±1.6d</td>
<td>−5.8±1.6d, −5.8±1.6d</td>
</tr>
</tbody>
</table>

Values are the means±SD or number (per cent). Group comparisons made using χ² and analysis of variance tests for categorical and continuous variables. P values for pairwise contrasts are Benjamini-Hochberg adjusted; values in a row not sharing subscript letters (a, b and c) denote subgroups whose averages differ significantly (p<0.05).

Table 2  Cross-tabulation of latent profile and traditional discordance groups

<table>
<thead>
<tr>
<th>Latent profiles</th>
<th>Traditional discordance categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low PtGA/low MDGA</td>
<td>Negative discordance</td>
</tr>
<tr>
<td>Moderate PtGA/moderate MDGA</td>
<td>3 (4.4%)</td>
</tr>
<tr>
<td>High PtGA/high MDGA</td>
<td>18 (26.5%)</td>
</tr>
<tr>
<td>High PtGA/low MDGA</td>
<td>0</td>
</tr>
<tr>
<td>Low PtGA/low MDGA</td>
<td>46 (67.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (11.0%)</td>
</tr>
</tbody>
</table>

All percentages are column percentages.

traditional discordance category. Group 1 (low
would, under usual circumstances, be collapsed into a
outcomes as shown in figure 3.

More importantly, they also reported diverse functional,
atory evaluations of inflammatory burden (table 2).
The LPA groups differed across all clinical and labo-
ical function, pain, fatigue, depression, HRQoL, work
and superior physical and mental function than group

(26.0%) and high PtGA/high MDGA group 3 (19.6%)
latent profiles.

The LPA group solution demonstrated significantly
higher explanatory power (adjusted incremental $R^2$)
for all inflammatory activity parameters, as well as phys-
function, pain, fatigue, depression, HRQoL, work
productivity and activity impairment outcomes than the
traditional discordance definition (figure 2, all p<0.001);
this was above and beyond that accounted for by age,
gender, RA duration, IAD and fibromyalgia.

Clinical, functional and HRQoL outcomes

The LPA groups differed across all clinical and labo-
atory evaluations of inflammatory burden (table 1).
More importantly, they also reported diverse functional,
HRQoL, work productivity and activity impairment
outcomes as shown in figure 3 and table 3.

This was particularly true for groups 1, 2, and 3, which
would, under usual circumstances, be collapsed into a
singular traditional concordance category. Group 1 (low
PtGA/low MDGA) reported the lowest burden of physical
impairment, pain, fatigue, depression, work productivity
and activity impairment and enjoyed near normal phys-
ical and mental function (compared with age-matched
and gender-matched norms). In contrast, group 3 (high
PtGA/high MDGA) fared the worst of all groups; it
reflected the highest inflammatory burden, greatest phys-
ical, mental and social function restrictions, along with
with worst pain, fatigue and depression scores. Group 4 (high
PtGA/low MDGA) patients experienced significant RA
impact despite low inflammatory burden. Surprisingly,
patients in group 5 (low PtGA/high MDGA) reported
significantly lower physical limitations, pain, fatigue,
depression, work productivity loss and activity impairment

DISCUSSION

Our study demonstrates the validity and advantages of
an empirically derived, person-centred approach charac-
terising the relationship between patient and physician
assessments of RA activity based on two simple measures
(PtGA and MDGA); both are collected in routine prac-
tice, represent ACR core set components and inform
therapeutic decisions.

We describe several novel findings: first, LPA yielded
a statistically robust five-profile solution representing
distinct patient groups with clinically meaningful pheno-
types. Second, the LPA-generated solution was quanti-
tatively and qualitatively distinct from the conventional
three-group discordance definition. This difference
stemmed mainly from heterogeneity in the traditional
concordance category regarding the magnitude of
disease activity patients and physicians consensually
report; despite congruent PtGA and MDGA ratings, LPA
groups 1, 2, and 3 represented clearly distinct patient
clusters with increasing inflammatory burden as well
as progressively worse clinical, functional, HRQoL,
work-related and activity impairment outcomes. These
three highly disparate, empirically defined groups were
essentially collapsed into a singular, conventional concor-
dance category, which was arbitrarily defined and—by
design—disregarded the absolute levels of the individual
PtGA and MDGA components. Hence, the lesson learnt
here was that all agreement is not created equal; rather, it
is the magnitude of the disease activity that both patients
and physicians concur on that largely defines functional
outcomes.

Third, when both parties report high disease activity
(group 3), there is objective evidence of high inflam-
matory burden and patients experience worse physical
function, pain, fatigue, depression, HRQoL, activity
impairment and work productivity than any other group.
This is in agreement with reported associations of high
RA inflammatory activity with worse fatigue, pain, and
physical disability. However, within

Figure 2  Explanatory power of the LPA solution for
clinical and functional outcomes compared with the
conventional threshold-based discordance definition.
Bar height represents the unique variance accounted in
each outcome by the LPA and traditional discordance
approaches after controlling for the effects of age, gender,
RA duration, irreversible articular damage and fibromyalgia
(incremental $\Delta R^2$). Error bars represent 95% CIs. DAS28-
ESR, 28 joint-based disease activity index with ESR; ESR,
erythrocyte sedimentation rate; HAQ-DI, Health Assessment
Questionnaire-Disability Index; LPA, latent profile
analysis; MDGA, physician global assessment of disease
activity; PHQ9, nine-item Patient Health Questionnaire; PtGA,
patient global assessment of disease activity; SF36-MCS,
Short Form 36 mental component score; SF36-PCS, Short
Form 36 physical component score; SJC, swollen joint
count; TJC, tenderness joint count; TJC, tenderness joint
count.

the context of a traditional concordance construct, patients and physicians unanimously reported high disease activity in only a minority of cases (73/373 or 19.6%). In fact, in the majority of instances (203/373 or 54.4%), both parties reported low or absent disease activity (group 1). As a result, the magnitude of adverse impact conferred by the high disease activity cluster 3 to the extended traditional concordance group outcomes may be grossly attenuated. Consistent with that notion, several recent studies using conventional definitions reported that patients with concordant PtGA and MDGA ratings experience better functional outcomes compared with those with positive discordance.4 37 38 Our results, however, clearly indicate that all such outcomes are significantly worse in group 3 that unanimously reported high disease activity compared with group 4 (high PtGA/low MDGA), closely resembling the conventional positive discordance cluster.

Fourth, our LPA results confirmed the presence of groups qualitatively resembling the arbitrarily defined positive and negative discordance groups: latent profiles 4 and 5, respectively; this allows continued confidence in previous research derived based on such methodologies, regarding descriptions of such group characteristics and outcomes. Nevertheless, both such groups are more strictly defined by LPA; specifically, LPA group 4 represents a more homogeneous group compared with the broader traditional positive discordance cluster that is contaminated up to 18.7% by patients from groups 1 and 2, both of whom have superior outcomes. LPA group 4 patients are older, with longer disease duration and higher prevalence of fibromyalgia than all other groups. Despite minimal inflammation, indistinguishable from group 1, they experience substantial RA impact: they report significantly higher pain, fatigue and depression that directly contribute to their high PtGA scores4 and
Table 3  Patient-reported clinical, functional and health-related quality of life outcomes for latent profiles

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Low PtGA/low MDGA (n=222)</th>
<th>Moderate PtGA/ moderate MDGA (n=115)</th>
<th>High PtGA/high MDGA (n=91)</th>
<th>High PtGA/low MDGA (n=144)</th>
<th>Low PtGA/high MDGA (n=46)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain VAS</td>
<td>2.1±0.1 a</td>
<td>5.0±0.2 b</td>
<td>6.9±0.2 c</td>
<td>6.4±0.2 d</td>
<td>3.8±0.3 e</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Fatigue VAS</td>
<td>2.0±0.2 a</td>
<td>4.5±0.2 b</td>
<td>6.0±0.3 c</td>
<td>5.2±0.2 d</td>
<td>3.0±0.4 e</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PHQ-9</td>
<td>3.5±0.4 a</td>
<td>6.5±0.5 b</td>
<td>10.6±0.6 c</td>
<td>8.9±0.5 d</td>
<td>4.7±0.8 e</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>0.8±0.1 a</td>
<td>1.4±0.1 b</td>
<td>1.8±0.1 c</td>
<td>1.5±0.1 b</td>
<td>1.3±0.1 e</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Activity impairment</td>
<td>27.6±1.7 a</td>
<td>56.8±2.3 b</td>
<td>72.8±2.6 c</td>
<td>62.4±2.1 b</td>
<td>43.2±3.7 e</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>43.7±0.6 a</td>
<td>32.4±0.8 b</td>
<td>26.9±0.9 c</td>
<td>30.9±0.7 b</td>
<td>36.4±1.2 g</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>49.0±0.6 a</td>
<td>40.3±0.9 b</td>
<td>35.3±1.0 c</td>
<td>38.4±0.8 b</td>
<td>45.7±1.4 g</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SF-36 domain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>60.9±1.7 a</td>
<td>37.9±2.3 b</td>
<td>30.8±2.6 c</td>
<td>38.4±2.1 b</td>
<td>47.0±3.7 g</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Role-physical</td>
<td>61.3±2.3 a</td>
<td>23.3±3.3 b</td>
<td>7.3±3.6 c</td>
<td>22.0±3.0 b</td>
<td>29.9±5.1 b</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>63.4±1.3 a</td>
<td>40.8±1.8 b</td>
<td>25.5±2.0 c</td>
<td>35.8±1.6 b</td>
<td>46.8±2.8 b</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>58.8±1.3 a</td>
<td>43.0±1.8 b</td>
<td>34.8±2.0 c</td>
<td>38.0±1.6 c</td>
<td>51.9±2.8 b</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>66.0±1.2 a</td>
<td>50.9±1.7 b</td>
<td>42.7±1.9 c</td>
<td>47.2±1.5 b</td>
<td>58.6±2.7 g</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>79.5±1.6 a</td>
<td>60.1±2.3 b</td>
<td>48.3±2.6 c</td>
<td>54.4±2.1 b</td>
<td>73.9±3.6 e</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Role-emotional</td>
<td>75.0±2.5 a</td>
<td>44.7±3.5 b</td>
<td>29.6±3.9 c</td>
<td>46.3±3.2 b</td>
<td>56.3±5.5 b</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>73.9±1.3 a</td>
<td>62.9±1.8 b</td>
<td>54.6±2.1 c</td>
<td>58.0±1.7 bc</td>
<td>73.6±2.9 a</td>
<td>&lt;0.001</td>
<td></td>
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Employed participants

<table>
<thead>
<tr>
<th></th>
<th>Low PtGA/low MDGA (n=82)</th>
<th>Mod PtGA/mod MDGA (n=40)</th>
<th>High PtGA/high MDGA (n=23)</th>
<th>High PtGA/low MDGA (n=24)</th>
<th>Low PtGA/high MDGA (n=17)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absenteeism</td>
<td>5.3±2.0 a</td>
<td>13.0±2.8 bc</td>
<td>18.7±3.7 bc</td>
<td>3.9±3.6 abc</td>
<td>5.9±4.2 abcd</td>
<td>0.006</td>
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<tr>
<td>Presenteeism</td>
<td>20.9±2.8 a</td>
<td>45.5±3.9 b</td>
<td>59.6±5.2 c</td>
<td>46.6±5.1 bcd</td>
<td>29.4±6.0 ab</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Work productivity</td>
<td>23.9±3.0 a</td>
<td>49.6±4.3 b</td>
<td>66.3±5.6 c</td>
<td>47.8±5.6 bc</td>
<td>30.0±6.5 ab</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values represent estimated marginal means and SEs. Analysis of covariance adjusted for age, sex, disease duration, irreversible articular damage and fibromyalgia. All pairwise comparisons are Benjamini-Hochberg corrected; values in a row not sharing subscript letters denote subgroups whose averages differ significantly.

HAQ-DI, Health Assessment Questionnaire Disability Index; MCS, Mental component summary; MDGA, physician global assessment of disease activity; PCS, physical component summary; PHQ-9, nine-item Patient Health Questionnaire; PtGA, patient global assessment of disease activity; SF-36, Short Form 36 Health Survey; VAS, visual analogue scale.

yield worse functional, HRQOL and work productivity outcomes, even after controlling for age, gender, disease duration, IAD and fibromyalgia. These subjects are more poised to benefit from psychological and/or behavioural interventions to attain comprehensive remission rather than pharmacological treatments targeting RA inflammation.30 Similarly, LPA group 5 is more homogeneous compared with the extended conventional negative discordance group, which is contaminated up to 31% by group 2 and 3 patients. Specifically, LPA group 5 subjects experience significantly lower functional impairment and disease impact than expected, despite high inflammatory burden. It is possible that more adaptive illness cognitions and effective coping mechanisms40 41 account for the significantly lower levels of pain, fatigue and depression that these patients report and contribute to their advanced social functioning, mental health, HRQOL and work productivity that resemble group 1 patients. Nevertheless, most physical function outcomes were still worse in group 5 compared with group 1 patients who were essentially at therapeutic target.

Fifth, the patient-centred LPA solution offered superior explanatory power for all disease-related parameters and outcomes of interest compared with the traditional discordance construct. This observation further supports its higher clinical relevance, validity and suitability in characterising the relationship between PtGA and MDGA. This is particularly notable since variable-oriented approaches, in general, show greater predictive power compared with person-oriented approaches.42 Our findings collectively suggest that the traditional consideration of the PtGA and MDGA relationship as a discordance or difference score (PtGA–MDGA)—although intuitively appealing and computationally convenient—is arbitrary, qualitatively restrictive and methodologically suboptimal for multiple reasons. First, it is subject to all the restrictions of a variable-centred approach such as assumptions of population homogeneity.
and non-empirically derived, artificial cut-offs. Second, difference scores are less reliable than either of their component measures; they are inherently ambiguous, as they combine into a single score constructs that are structurally and functionally disparate; they confound the effects of their component measures on outcomes and impose constraints on these effects that are rarely tested empirically; correlations between difference scores and outcomes are often spurious as they essentially reflect the correlation of an outcome with the components from which the difference score is calculated. Since difference scores tend to correlate with either one or both of their components, the chances of observing correlations with other constructs connected to those components are amplified. Third, in the qualitatively distinct LPA solution, the number of latent groups that best fits the data is determined statistically rather than subjectively.

Hence, if one’s intention is to examine the relationship between PtGA and MDGA, LPA represents a less biased and more insightful way to visualise the spatial positioning of patients across the two outcomes, beyond the problems and biases of arbitrary difference scores. However, LPA analyses may not be the most practical solution for the routine group assignment of patients based on PtGA and MDGA in daily clinical practice. The analyses are generally complex to conduct and are sample and sample size specific, in that they yield groups that may differ from study to study. The most salient point, however, is that each of the two outcomes has its own significance and therapeutic implications and therefore commands individual attention and consideration; PtGA being a broader indicator of disease impact and experience by the patient and MDGA as a barometer of inflammatory burden. We previously reported that the most significant, independent predictors of PtGA were pain (27%), fatigue (15%), depression (9%), functional impairment (8%), general health perceptions (7%) and tender joint counts (6%). Notably, improvement of PtGA over time was associated with commensurate improvements in the same exact parameters. Consequently, disaggregation of domains within the PtGA should be contemplated to develop management pathways targeting optimal patient-centred outcomes.

This would be particularly true in the case of moderate or high PtGA, where illuminating the exact contribution of each of the aforementioned variables may yield a mixture of both biomedical as well as psychological/behavioural/cognitive interventions. Future research should inform a feasible, time-efficient set of patient-reported outcomes and define how to best integrate them into daily practice. The findings should foster a standardised approach to evaluation and management, as well as improvement of patient–physician communication and shared decision making. However, we showed that MDGA bore significant correlation with composite disease activity scores such as 28 joint-based disease activity index with ESR ($r=0.85$), and its improvement over time reflected improvement in swollen joint counts, tender joint counts, fatigue and ESR. The implications of MDGA are, therefore, largely biomedical, an arena most rheumatologists feel more comfortable navigating.

The current work has important implications for rheumatology research: existing discordance data may be reanalysed in an effort to enrich findings already published in the literature; this may include derivation of LPA algorithms in training sets and their validation in test populations. Prevalent datasets may be combined into a unique body of evidence with the intention to cross-validate congruence relationships using LPA. This might represent a more comprehensive attempt to reveal complexities in disease state definition by patient and physicians that have eluded empirical investigation due to the use of difference scores.

Several limitations of our study should be acknowledged: first, LPA was used as an exploratory approach in our study; therefore, replication of our findings in independent samples is necessary. Although we considered validation in an independent sample within our patient population, this was not feasible; despite the absence of a formal approach in the literature for the definition of sample size requirements for the performance of LPA, a size of at least 500 seems to be a general consensus for best practice. Our cohort, representing a single centre, is not large enough to generate the requisite sample size for a separate validation set. It is encouraging, however, that a recent large study from the Early Rheumatoid Arthritis Network and British Society of Rheumatology Biologics Register revealed identical patient groupings to ours using a similar LPA approach. Second, since findings were based on a sample of Hispanic whites from the USA, our results may not be generalisable to other RA patient populations. Third, given the cross-sectional nature of our study, caution is recommended in interpreting the predictive power of the latent profiles as causal relationships cannot be inferred. Future research should examine the stability and longitudinal trajectories of latent profiles and their associations with clinical, functional and HRQoL outcomes. Fourth, physicians were blinded to PtGA scores and all patient-reported outcomes at the time of their MDGA assessment in our study; although this could theoretically impact the results, it is consistent with clinical trial practices and allows for a more impartial physician rating.

**CONCLUSION**

An unbiased, empirically derived, patient-centred LPA approach to characterise the relationship between patient and physician assessments of disease activity identified distinct, homogeneous and clinically meaningful patient groups. The five-profile solution was quantitatively and qualitatively distinct from the traditional threshold-based discordance definition; it confirmed that the magnitude of disease activity consensually reported by patients and physicians is a pivotal determinant of functional outcomes and demonstrated greater predictive power.
for disease-related, clinical, functional and HRQoL outcomes. Further validation of our findings may corroborate its clinical relevance, validity and suitability characterising the relationship between PtGA and MDGA.

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Contributors  All authors were involved in the study design and/or collection, analysis and interpretation of the data, provided critical revision of the manuscript and approved the final version to be submitted for publication.

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