The Clinical Disease Activity Index (CDAI) and the Routine Assessment of Patient Index Data3 (RAPID3) for Achievement of Treatment Strategies

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Abstract

Objective. To compare the CDAI with the RAPID3 from two large US Registries.
Methods Using a cross section of clinic visits within two registries we determined if the outcome of each metric would place the patient in remission (R), low (LDA), moderate (MDA), or high disease activity (HDA) using a CDAI with the assumption that a patient in MDA or HDA would be a candidate for acceleration of treatment.
Results We identified significant disparities between the two indices in final disease categorization using each index system. For patients identified in LDA by CDAI, RAPID3 identified 20.4% and 28.3% as LDA in Corrona and BRASS respectively. For patients identified as MDA by CDAI, RAPID3 identified 36.2% and 31.1% as MDA in Corrona and BRASS respectively with the greatest disparities within each system identified for LDA and MDA activity by the CDAI (20.4% and 36.2% agreement of RAPID3 with CDAI respectively in Corrona and 28.3% and 31.1% agreement in BRASS). Overall comparison between CDAI and RAPID3 in the 4 disease categories resulted in estimated Kappa=0.285 in both.
The RAPID3 scores indicated the potential for treat to target acceleration in 34.4% of patients in remission or LDA based on CDAI in Corrona and 27.6% in BRASS respectively
Conclusion The RAPID3, based on patient reported outcomes, shows differences with CDAI categories of disease activity. The components of CDAI are not highly correlated with RAPID3 except for patient global. These differences could significantly impact the decision to advance treatment when using a treat to target regimen.

Introduction

Metrics are essential for evaluating disease activity in patients with Rheumatoid Arthritis. Given that rheumatologists have accepted the widely held approach of “treating to target” (1,2), it is apparent that measures that accurately reflect disease activity in RA are critical for management decisions regarding maintaining, changing, or adding treatment regimens in order to achieve the desired target of low disease activity or remission (1,2)
The DAS28ESR and DAS28CRP are accepted as a gold standard along with the American College of Rheumatology (ACR) 20, 50 and 70 responses. (3) However, it is widely recognized that these measures required for regulatory approval are not widely utilized in routine clinical practice in the US given their complexity and diligence needed to perform them in the course of routine care. In addition, the acute phase reactant is not available at the time of the clinic visit.

The Clinical Disease Activity Index (CDAI) is another validated metric that can actually be calculated at the same time as a clinical encounter as it is the simple sum of the number of tender and swollen joints along with the numerical value of both a patient and physician global

activity on a visual analogue scale (4,5). Another metric that has become widely used is the RAPID3 (6,7) that employs values obtained directly from the patient without physician input.

However, recent publications have questioned the contribution of the patient-derived pain and global activity (9-18) with the latter measure found in both metrics. The RAPID3 will of course derive its final score from patient evaluations as this metric is not associated with either a physician examination or an acute phase reactant, but only a patient pain and global arthritis activity score along with a HAQ. The CDAI is derived from a simple summary of a 28 tender and swollen joint count along with a physician and patient global score.

It is relevant that a significant disparity has been found between patient assessment of pain and global arthritis activity and other measures of disease activity (8-17). Several publications have found that factors other than disease activity affect these core components of the RAPID3 metric. These elements include depression, life satisfaction and anxiety that may be ongoing and independent of control of inflammation (18-22). It has been suggested that patient pain and global disease activity scores measure different domains of patient welfare (23-30).

We thus sought to compare the CDAI and RAPID3 scores on patients along with analyses of the individual components of each metric to better understand their contribution to the final score within each system. We used two different registries in the United States including one from primarily geographically diverse community rheumatologists and one from an academic practice collecting these prospective metrics at the time of a clinical encounter. We focused on how the different measures would inform treatment decisions if they were used in everyday clinical practice while also determining which components of each final metric are potentially problematic for making decisions to treat ongoing inflammation.

Methods

All participating investigators were required to obtain full board approval for conducting research involving human subjects. Sponsor approval and continuing review was obtained through a central IRB (New England Independent Review Board, NEIRB No. 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective governing IRBs and documentation of approval was submitted to the Sponsor prior to initiating any study procedures. All registry subjects were required to provide written informed consent prior to participating.

Data Sources

The registry, known as the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS), began recruitment in 2003. Subjects older than 18 years of age were recruited from the Arthritis Center practices of attending rheumatologists and fellows All diagnoses of RA were either verified according to the 1987American College of Rheumatology (ACR) criteria by a rheumatologist or met the rheumatologists' impression for a diagnosis of RA. Subjects were evaluated by their rheumatologists yearly where information about demographics, medication use, disease activity, functional status and comorbidities were obtained. Currently 1343 have

baseline data enrolled in the study. Details related to the participation and protocol in the BRASS Registry has been reported elsewhere (31).

The Corrona RA registry, founded in 2000, includes a network of greater than 700 participating academic and community rheumatologists at over 180 sites in more than 40 states within the US. All patients with a diagnosis of RA treated by participating rheumatologists are eligible to be included in Corrona. Data are gathered at clinical visits from patient and provider forms as has previously been described (32).

Data from the most recent visit of 48,255 were extracted from 184 Corrona registry sites (83% private and 17% academic) in 42 states to perform a cross-sectional analysis. The visit dates ranged from 10/2/2001 – 8/30/2019.

The Corrona Rapid3 (cRAPID3) is a modified RAPID3 scale used for this study. It does not include the following two items which are not collected by the Corrona registry: 1) Are you able to walk two miles or 3 KM if you wish, and 2) Are you able to participate in recreational activities and sports as you would like, if you wish? The scoring of the remaining 8 "Are you able to …" items of the RAPID3 were weighted to ensure the cRAPID3 score was on the same scale as the RAPID3 (0-10). The patient pain and patient global health components of the RAPID3 were not re-weighted, and the cRAPID3 score ranged from 0-30. The cRAPID3 was also computed in the BRASS registry for comparative purposes.

Rate of MDA/HAD by cRAPID3 for those in CDAI remission/LDA were compared between biologic experienced and naïve using logistic regression model and adjusted for duration of disease (early ≤2yrs) vs late (>2 yrs)) at time of the measurement.

Disease Activity Categories

RA disease activity was measured using CDAI and cRAPID3 in Corrona. A CDAI of 2.8 or less was classified as remission, greater than 2.8 but less than or equal to 10 was classified as low disease activity (LDA), greater than 10 but less than or equal to 22 was classified as moderate disease activity (MDA), and greater than 22 was classified as high disease activity (HDA). Similarly, for RAPID3 and cRAPID3 of 3 or less was classified as remission, greater than 3 but less than or equal to 6 was LDA, greater than 6 but less than or equal to 12 was MDA, and greater than 12 was HDA.

Statistical Methods

Spearman correlation coefficients (no assumptions of normality) were calculated to assess the correlation between CDAI, cRAPID3 and RAPID3 as well as individual measurements of clinical characteristics and disease activity levels. Kappa statistics were calculated to determine the relationship between CDAI and cRAPID3 classifications (Remission, LDA, MDA, and HDA). Additionally, Kappa statistics were also calculated to determine the relationship between the potential treat to target groups (Remission and LDA vs. MDA HDA) measured by CDAI and cRAPID3.

Results

There are 48,255 Corrona RA patients with CDAI and cRAPID3 measures, and 1,343 BRASS RA patients with CDAI and RAPID3 measures. Patient demographics and clinical disease measures are in Table 1. BRASS RA patients are younger (55.9yrs vs 61.9 yrs), have higher mean CDAI (19.5 vs 11.3) but slightly lower cRAPID3 (7.3 vs 8.2). MD Global Assessments are higher in BRASS (30.6 vs 19.6) but Patient Global Assessments are lower (31.7 vs 49.9).

We found that the RAPID3 and cRAPID3 have a high correlation (spearman r=0.998) and overall agreement across disease activity categories is 94% [Table 2] and as measured by a kappa statistic that accounts for chance agreement (kappa=0.92).

Comparison of CDAI and cRAPID3 disease categories in both registries is illustrated in Figure 1 and Tables 3a and 3b with kappa = 0.28 and 0.24 for Corrona and BRASS, respectively. Both registries show high proportion of cRAPID3 remission within CDAI remission group (78% Corrona, 87% BRASS) but more disagreement at other disease activity levels. For example, only 32% (Corrona) and 41% (BRASS) of CDAI MDA are classified as MDA by cRAPID3. As seen in the figure and tables, results are similar for comparison of CDAI and RAPID3 in BRASS.

Collapsing categories combining MDA and HDA for indication of potential treatment acceleration and remission and LDA for indication of no potential treatment acceleration agreement of CDAI and cRAPID3 are shown in Table 4 (kappa= 0.46 Corrona and .39 BRASS). Both registries show close to one-third - 35% (Corrona) and 28% (BRASS) – cRAPID3 indicating potential acceleration while CDAI indicates remission/LDA.

The correlation of CDAI, cRAPID3 and RAPID3 along with components of the measures are shown in Table 5ab for Corrona and BRASS. CDAI and cRAPID3 have estimated spearman correlation of r= 0.72 (Corrona) and 0.58 (BRASS). As would be expected given the lesser contribution of this metric to the calculation of the CDAI, Patient Global Assessment (PGA) has a higher correlation with RAPID3 and cRAPID3 (.94 Corrona .91 BRASS both cRAPID3 and RAPID3) than CDAI with PGA (.71 Corrona, .58 BRASS cRAPID3 .57 RAPID3). MD Global Assessment, not found in the RAPID3, correlated more highly with CDAI (.78 Corrona, .81 BRASS) than cRAPID3 (.47 Corrona, .56 BRASS) and RAPID3 (.57 BRASS). Tender and Swollen Joint Counts, not found in the RAPID3, correlated more highly with CDAI (TJ .80 SJ .74 Corrona; TJ .90 SJ .85 BRASS) than cRAPID3 or RAPID3 (TJ .48 SJ .31 Corrona cRAPID3; TJ .44 SJ 2.9 BRASS cRAPID3; TJ.44 SJ: .30 BRASS RAPID3) while patient pain, not found in the CDAI but present in the RAPID metrics, correlated more highly with cRAPID3 and RAPID3 (.94 Corrona cRAPID3; .92 BRASS cRAPID3; .92 BRASS RAPID3) then CDAI (.67 Corrona; .50 BRASS) (Table 5ab)

The comparison of CDAI to cRAPID3 was examined by disease duration and by biologic naïve vs experienced (supplemental Tables S1 and S2). Rates of cRAPID3 in MDA/HDA among those with CDAI remission/LDA were slightly higher in the biologic experienced vs naïve (38% vs 30% Corrona, 30% vs 28% BRASS). Adjusted for duration of disease the difference by biologic experience was significant (p<0.001 Corrona, 0.046 BRASS)

Discussion

We found poor correlations in both registries between RAPID3 (or cRAPID3) and CDAI scores for patients in CDAI LDA and MDA while the congruence for both between the metric final scores of remission and HDA were better. When considered together these data indicate that patient derived measures contribute differently to the metrics dominating the RAPID3, while both swollen and tender joints and the physician global scores dominate the CDAI (r=0.741, 0.803 and 0.788 respectively in Corrona and 0.851, 0.902 and 0.805 in BRASS, TABLE 5).

While it might at first appear to be somewhat circular reasoning, or an obvious predetermined outcome, to derive correlations of components found selectively within only one of the two metrics with final scores of both metrics, we believe that it serves a larger purpose. Both the CDAI and the RAPID3 are presently being used to inform treatment decisions. If patients are to be managed based upon the results of these scores then an understanding of what the components represent, and their relative contribution to the final score, is relevant.

Our approach in comparing the CDAI with the RAPID3 (or cRAPID3) was to compare the different final metrics to each other. We believed that it was appropriate to identify the CDAI as the acceptable core clinical outcome metric as has previously been established (4,5). Because we had simultaneous outcome metrics from both registries obtained at the same visit from all patients there was an unusual juxtaposition of circumstances to facilitate comparison of the real-world performance of the RAPID3 to the CDAI.

A rich recent literature has well- described the psychological and life satisfaction factors that contribute so strongly to patient-derived measures of the RAPID3 including the patient global and pain score (9-23). It is apparent that the RAPID3 can provide a clinician with potentially complementary information on the welfare of their patient. But, as has been demonstrated in these recent publications, because the RAPID3 is dominated by parameters with strong psychological and psychosocial derivations the scores should not be used in isolation to either evaluate ongoing RA inflammation or to adjust treatment. Ferreira and colleagues have suggested a “dual-target approach” in which psychological outcomes are derived from patients while inflammation-related variables are derived from physician joint counts as found in a CDAI (33).

We believe that it is thus important to recognize that even though certain key variables such as tender and swollen joints on examination as well as a physician global evaluation are not found in the RAPID3 that their absence should not release this metric from the burden of achieving the goal of reflecting inflammatory disease activity as captured in a validated metric such as the CDAI. As several authors have described, these patient-reported outcomes reflect different domains of patient welfare (23-30). Additional compelling evidence from a Dutch society published by Boone and colleagues has described similar disparities between the RAPID3 and both the CDAI (34) and the DAS28 (35).

The high correlation and agreement of RAPID3 and cRAPID3 provides evidence that the cRAPID3 used in Corrona is a good proxy for RAPID3. We thus employed the cRAPID3 in Corrona to derive correlations with the CDAI after confirming the very high correlation with the full RAPID3 in BRASS (Table 2). The metrics from the Corrona registry were collected from 706 rheumatologists at 184 sites in 42 different states with a distribution of private vs academic sites of 83% to 17% respectively. The results for each metric were compared both within and across registries. The BRASS registry represents data that are entirely derived from a single academic center. We found that there were differences in the evaluation of disease activity between registries. The patient global scores are quite similar while the physician global evaluations differ (19.26 [20.40] and 30.28 [21.79] in Corrona and BRASS respectively) as do the CDAI scores (11.24 [11.50] and 19.47 [16.45]) respectively). The reasons for the differences are speculative but may reflect either the likelihood that a tertiary academic center might attract more challenging patients or the fewer numbers of evaluators in BRASS. We did not have an a priori expectation that the disease activity would be overwhelmingly similar in both Corrona and BRASS given the differences in the makeup of the registry sites and we believed that this was a virtue when comparing the CDAI with the RAPID3. Nevertheless, the reason(s) for the differences in the physician global score remain speculative. The differences in these ratings may indeed be site specific and reflect a shared approach for disease assessment of providers at a single site. Differences in Physician Global evaluation might be a topic for future research.

While the RAPID3 is convenient and saves physician time compared with a 28 joint count and physician global score, it is apparent that the outcome scores are frequently divergent from the CDAI. In addition, it has recently been published that the same RAPID3 can be used to reflect osteoarthritis (OA) disease activity (35). Given that patients with RA often have concomitant OA it would not be possible to determine the contribution of OA disease to the patient's rating of pain and global arthritis activity when the same metric is used for RA.

The study has several strengths. We studied a very large number of patients and compared the CDAI and cRAPID3 measures obtained at the time of the same clinic visit. We compared data across two different registries including one from an academic health science center (BRASS) and one from predominantly private practitioners (Corrona). In addition, we were able to examine the correlation of the patient global and pain measures with each metric and confirm the discordance with an array of clinical disease measures obtained by a physician. For what we believe is the first time, we extend earlier findings on patient pain and global evaluations as they apply to a commonly used patient-derived metric, the RAPID3, in comparison with a CDAI.

There are also some potential weaknesses. Physician tender and swollen joint counts were typically performed by the same clinician but not always. The Corrona registry consists of multiple sites with inevitable variability across sites while BRASS is a single academic site with fewer evaluators. It is possible that differences in results between the registries reflect these differences in site composition. These analyses are derived from a cross-sectional, retrospective review of prospectively collected observational data. Nevertheless, the inclusion of the possibility of different investigators evaluating the same patient might actually add to the

representativeness of the observations across different physicians thus hypothetically buttressing the external validity of the data. We believe that the heterogeneity of the data sources and very large number of clinical evaluations from two different registries serves to support the clinical conclusion. It is also possible that these US-based findings may not be representative of other societies although we believe that this is not likely as much of the data we cite on the discordance of the patient global with actual disease activity are derived from European authors (9-12, 14-17, 19, 20-23).

In conclusion, the RAPID3 should not be used as an exclusive measure to evaluate clinical status and inform treatment decisions as the individual components of this metric are highly associated with non-inflammatory conditions such as depression, anxiety and quality of life (19-23) and are discordant with CDAI evaluations. Nevertheless, the RAPID3 can add valuable information on patient psychometrics that complement the CDAI outcomes that are more reflective of inflammatory outcomes. We believe that it is important that treating clinicians recognize and acknowledge the core clinical themes that are actually being measured within each metric. A patient who is doing well on a CDAI, but not on a RAPID3, should be further evaluated for the contribution of both psychosocial factors and OA to this score and it should not be relied upon to adjust treatments using a treat to target pathway.

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Table 1: Patient Characteristics at index date in each registry

	CORRONA	BRASS
N	48,255	1343
Age (years): Mean (SD)	61.73 (13.91)	55.90 (14.16)
Gender		
%Female	76.36	82.20
Duration of Disease (yrs): Median (IQR)	9 (4, 17)	8 (3, 19)
Swollen joint count: Mean (SD)	2.71 (4.42)	6.20 (7.05)
Tender joint count: Mean (SD)	3.35 (5.46)	7.04 (7.71)
Patient Global Assessment: Mean (SD)	32.58 (27.41)	31.67 (25.18)
MD Global Assessment: Mean (SD)	19.26 (20.40)	30.58 (21.79)
CDAI: Mean (SD)	11.24 (11.50)	19.47 (16.45)
Disease Activity		
% Remission (CDAI ≤2.8)	25.34	12.51
% Low (2.8<CDAI≤10.0)	34.74	26.81
% Moderate (10.0<CDAI≤22.0)	24.75	24.65
% Severe (CDAI>22)	15.17	36.04
RAPID3: Mean (SD)	NA	7.62 (5.45)
RAPID3 Disease Activity Categories		
% Remission (RAPID3 ≤3.0)	NA	26.06
% Low (3.0<RAPID3 ≤6.0)	NA	19.96
% Moderate (6.0<RAPID3≤ 12.0)	NA	31.94
% Severe (RAPID3> 12.0)	NA	22.04
cRAPID3*: Mean (SD)	8.15 (6.55)	7.29 (5.35)
cRAPID3 Disease Activity Categories		
% Remission (RAPID3 ≤3.0)	31.22	28.74
% Low (3.0<RAPID3 ≤6.0)	14.82	19.14
% Moderate (6.0<RAPID3 ≤12.0)	25.09	31.57
% Severe (RAPID3> 12.0)	28.87	20.55
Patient Pain: Mean (SD)	35.11 (28.84)	34.56 (27.32)
Patient Reported Fatigue: Mean (SD)	38.00 (30.47)	41.41 (29.41)

*cRAPID3 is RAPID3 computed within Corrona registry without two of the HAQ questions, rescaled to 0-30

Table 2: Agreement of Disease Activity Levels of cRAPID3 and CDAI from Corrona and BRASS registries

		CORRONA			
		cRAPID3* categories			
		REM	LDA	MDA	HDA
CDAI categories	REM	9,584 (78.4%)	2,017 (16.5%)	603 (4.9%)	25 (0.2%)
	LDA	3,999 (23.9%)	3,414 (20.4%)	6,060 (36.2%)	3,289 (19.6%)
	MDA	1,235 (10.3%)	1,330 (11.1%)	3,835 (32.1%)	5,542 (46.4%)
	HDA	248 (3.4%)	388 (5.3%)	1,610 (22.0%)	5,076 (69.3%)
		BRASS			
		cRAPID3* categories			
		REM	LDA	MDA	HDA
CDAI categories	REM	146 (86.9%)	16 (9.5%)	6 (3.6%)	0 (0%)
	LDA	118 (32.8%)	102 (28.3%)	112 (31.1%)	28 (7.8%)
	MDA	69 (20.9%)	66 (19.9%)	134 (40.5%)	62 (18.7%)
	HDA	53 (11.0%)	73 (15.1%)	172 (35.5%)	186 (38.4%)

***Percentages are row percents showing percent of cRAPID3 categories within each CDAI category. Kappa statistic of agreement 0.237 (Corrona) and 0.242 (BRASS)**

Table 3: Comparison of potential "Treat to Target" indication in Corrona and BRASS. CDAI and cRAPID3 disease categories dichotomized into remission/LDA and moderate/high disease activity.

CORRONA			
		cRAPID3*	
		No acceleration (REM/LDA)	Potential Acceleration (MDA/HDA)
CDAI	No acceleration (REM/LDA)	19,014 (65.6%)	9,977 (34.4%)
	Potential Acceleration (MDA/HDA)	3,201 (16.6%)	16,063 (83.4%)
BRASS			
		cRAPID3*	
		No acceleration (rem/LDA)	Potential Acceleration (MDA/HDA)
CDAI	No acceleration (rem/LDA)	382 (72.35%)	146 (27.65%)
	Potential Acceleration (MDA/HDA)	261 (32.02%)	554 (67.98%)

*cRAPID3 is RAPID3 computed within Corrona registry without two of the HAQ questions, rescaled to 0-30. Row percentages showing percent of cRAPID3 categories within each CDAI category. Moderate/High disease is labeled as a potential indication patient should have accelerated treatment. Kappa agreement statistics: 0.492 (Corrona) and 0.388 (BRASS)

Table 4: Spearman Rank correlations of CDAI, cRAPID3* and components within the Corrona and BRASS registries. P-values testing correlations equal to zero are all <0.001.

CORRONA

	CDAI	Rapid3	cRapid	Pt Global	MD Global	Tender Jt	Swollen Jt	Pt Pain	MDHA Q score
CDAI	1.000								
RAPID3	NA								
cRapid	0.721	NA	1.000						
Pt Global	0.711	NA	0.942	1.000					
MD Global	0.783	NA	0.468	0.435	1.000				
Tender Jt	0.803	NA	0.477	0.438	0.626	1.000			
Swollen Jt	0.741	NA	0.311	0.289	0.578	0.561	1.000		
Pt Pain	0.670	NA	0.943	0.843	0.449	0.464	0.297	1.000	
MDHAQ score	0.538	NA	0.772	0.641	0.374	0.386	0.252	0.629	1.000

BRASS

	CDAI	Rapid3	cRapid	Pt Global	MD Global	Tender Jt	Swollen Jt	Pt Pain	MDHA Q score
CDAI	1.000								
RAPID3	0.579	1.000							
cRapid	0.572	0.998	1.000						
Pt Global	0.542	0.911	0.911	1.000					
MD Global	0.806	0.566	0.563	0.504	1.000				
Tender Jt	0.902	0.444		0.385	0.692	1.000			
			0.438						
Swollen Jt	0.851	0.296	0.289	0.253	0.603	0.685	1.000		
Pt Pain	0.496	0.919	0.923	0.709	0.524	0.401	0.260	1.000	
MDHAQ score	0.539	0.766	0.745	0.651	0.506	0.442	0.330	0.630	1.000

*cRAPID3 is RAPID3 computed within Corrona registry without two of the HAQ questions, rescaled to 0-30

Figure 1:

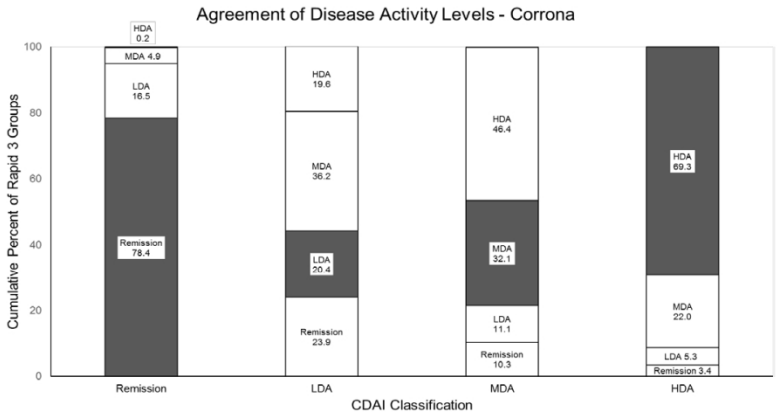

Figure 1: Illustration of distribution of cRAPID3 categories within each CDAI category for the Corrona registry. Darker section shows area of agreement. For example, for CDAI remission, 78.4% cRAPID3 also indicated remission. cRAPID3 is RAPID3 computed within Corrona registry without two of the HAQ questions, rescaled to 0-30.

215x279mm (150 x 150 DPI)

Figure 2

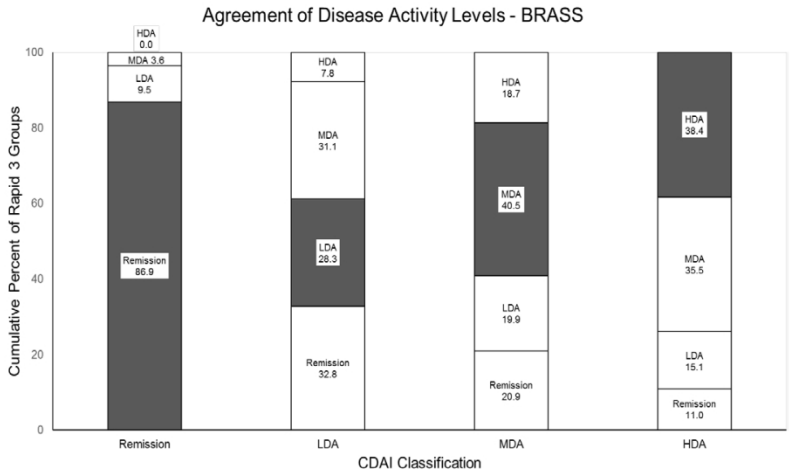

Figure 2: Illustration of distribution of cRAPID3 categories within each CDAI category for the BRASS registry. Darker section shows area of agreement. For example, for CDAI remission, 78.4% cRAPID3 also indicated remission. cRAPID3 is RAPID3 computed within Corrona registry without two of the HAQ questions, rescaled to 0-30.

215x279mm (150 x 150 DPI)