Supplementary file for the paper:

Patient clustering by serum inflammatory mediators stratifies early disease-modifying anti-rheumatic drug-naive rheumatoid arthritis and reveals distinct pathobiological signatures: a prospective observational cohort

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Supplementary data

Elastic net regression to model the association between mediator changes and clinical response

To model the association between inflammatory mediator changes and the 24-week change in CDAI (ΔCDAI), we employed a regularised regression analysis stratified by patient cluster. The predictors were the Z-standardised, log-transformed changes in 13 serum mediators from baseline to 24 weeks. Values below the lower limit of detection (LOD) were treated as left-censored and imputed using multiple imputation by fully conditional specification (FCS-MI; m=20 datasets). The analysis was performed on a complete-case basis for the outcome, ΔCDAI.

A two-stage modelling strategy was used to identify a stable subset of influential mediators. First, an elastic net model with a grid of α values {0, 0.25, 0.5, 0.75, 1} was trained in each imputed dataset. The model was tuned using nested 10-fold cross-validation, and the lambda.1se rule was applied for parsimonious variable selection. Predictors with a high selection frequency across imputations were considered stable. Second, a standard multiple regression model including only these stable predictors was fitted to each dataset. The resulting coefficients and 95% confidence intervals (CIs) were then pooled using Rubin's rules to generate final estimates. Primary interpretation was based on the pooled 95% CIs, with FDR-adjusted *p*-values calculated as a supportive measure.

Supplementary Table S1. Treatment exposure by cluster during weeks 24–52.

	Cluster 1 (n=106)	Cluster 2 (n=78)	Overall (n=184)
Treatments (24 weeks to 52 weeks)			
MTX, n (%)	81 (76.4)	64 (82.1)	145 (78.8)
bDMARDs, n (%)	21 (19.8)	22 (28.2)	43 (23.4)
TNFi, n (%)	15 (14.2)	11 (14.1)	26 (14.1)
IL-6Ri, n (%)	4 (3.8)	2 (2.7)	6 (3.3)
CTLA4-Ig, n (%)	0 (0.0)	5 (6.4)	5 (2.7)
JAK inhibitor, n (%)	0 (0.0)	2 (2.6)	2 (1.1)
Mulitple classes, n (%)	2 (1.9)	2 (2.6)	4 (2.2)
Glucocorticoid, n (%)	19 (17.9)	13 (16.7)	32 (17.4)
Glucocorticoid dose for users (prednisolone equivalent, mg/day)	2.00 [1.00, 3.00]	2.0 [1.00-2.50]	2.00 [1.00-3.00]

Data are presented as n (%) for proportions and as median [IQR] for doses. Denominators include patients with available 24-week serum data (n=184; Cluster 1=106, Cluster 2=78). “Any use” percentages are calculated using these denominators; doses are summarised among users only. Glucocorticoid dose as is reported daily prednisolone-equivalent (mg/day).

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; CTLA4-Ig: cytotoxic T-lymphocyte antigen 4-immunoglobulin; DMARDs: disease-modifying anti-rheumatic drugs; IL-6Ri: interleukin-6 receptor inhibitor; JAKi: Janus kinase inhibitor; MTX: methotrexate; TNFi: tumour necrosis factor inhibitor

Supplementary Table S2. Consensus-based diagnostics for selecting the number of clusters (k=2-4).

k	PAC	Within consensus	Between consensus	Consensus CDF (AUC)	ΔAUC from prev.	Silhouette (median [Q1–Q3])	Min cluster proportion (median [Q1–Q3])
2	11.1%	0.958	0.043	0.495	–	0.306 [0.303–0.309]	42.9% [41.5%–43.8%]
3	22.3%	0.897	0.071	0.587	0.092	0.165 [0.154–0.205]	18.9% [14.7%–20.6%]
4	37.7%	0.746	0.097	0.725	0.138	0.140 [0.136–0.146]	17.6% [10.3%–18.8%]

PAC = share of off-diagonal pairwise consensus values in (0.10, 0.90). Within/Between = mean consensus for pairs within *vs.* between final clusters (final labels from Ward.D2 on 1 − consensus). Consensus CDF (AUC) = area under the empirical CDF of off-diagonal consensus values 0–1; ΔAUC = change from the previous k (NA at k=2). Silhouette (median) = median of mean silhouette widths across imputations (Euclidean distance, Ward.D2 linkage). Min cluster proportion (median) = median of the smallest cluster size / N across imputations.

PAC: proportion of ambiguous clustering (share of pairwise consensus in (0.10: 0.90)); Within/Between: mean within-cluster / between-cluster consensus; CDF: cumulative distribution function; AUC: area under the curve (of the consensus CDF); ΔAUC: change in AUC from the previous k; k: number of clusters

Supplementary Table S3. Sensitivity analysis: concordance of alternative hierarchical settings with the primary solution (k =2)

	ARI, median	ARI, Q1	ARI, Q3
Eucidean + Ward.D2	1.000	1.000	1.000
Manhattan + Average	0.813	0.777	0.867
Manhattan + Complete	0.693	0.641	0.764
Correlation + Ward.D2	0.319	0.298	0.330

Each alternative partition was compared to the primary reference partition (Euclidean distance + Ward.D2 linkage, k=2) using the Adjusted Rand Index (ARI) across the 20 imputed datasets. Values are summarised as median [interquartile range]. The low ARI for the correlation-distance + Ward.D2 combination reflects an expected method-metric mismatch, as Ward's criterion is optimised for Euclidean space.
ARI: Adjusted Rand Index; Ward.D2: Ward's minimum-variance linkage (defined for squared Euclidean distances); Q1: first quartile (25th percentile); Q3: third quartile (75th percentile)

Supplementary Table S4. Performance and comparison of logistic regression models for predicting Cluster 1

Model	Predictors Included	AUC [95% CI]	AIC	BIC	Hosmer-Lemeshow (*p*-value)
Model A	CRP	0.527 (0.442–0.613)	248.4	254.7	0.552
Model B	RF	0.785 (0.717–0.852)	201.5	207.8	0.548
Model C	Age + RF	0.784 (0.717–0.851)	203.3	212.8	0.919
Model D	Age + CRP + RF	0.791 (0.725–0.858)	203.4	216.1	0.632
Model E	Age + CRP + RF + ACPA	0.794 (0.727–0.860)	205.4	221.2	0.757

Models are logistic regressions predicting Cluster 1 membership (binary outcome). AUCs are reported with 95% confidence intervals using DeLong's method; Hosmer-Lemeshow goodness-of-fit *p*-values are shown; lower AIC/BIC indicate better fit/parsimony. Predictors were transformed as follows: CRP as log (CRP + 0.001), RF and ACPA as log (value + 1); age is in years. All analyses used complete cases, and ROC/AUC estimates were computed on the same analysis set. Pairwise AUC comparisons among key models (B *vs.* D, B *vs.* E, C *vs.* D, D *vs.* E) using DeLong's test were not statistically significant (all $p>0.25$)

ACPA: anti-citrullinated protein antibody; AIC: Akaike information criterion; AUC: area under the ROC curve; BIC: Bayesian information criterion; CI: confidence interval; CRP: C-reactive protein; RF: rheumatoid factor.

Supplementary Table S5. Baseline characteristics by availability of the 24-week serum sample (missing at 24w *vs.* available at 24w).

		Missing at 24w (n=20)	Available at 24w (n=184)	SMD
Age at diagnosis, median [IQR]		70.00 [46.00, 77.25]	68.00 [57.00, 75.50]	0.220
Female sex, n (%)		17 (85.0)	115 (62.5)	0.529
RF positivity, n (%)		17 (85.0)	132 (71.7)	0.326
RF titer (IU/mL), median [IQR]		54.15 [18.28, 117.35]	61.40 [18.97, 145.50]	0.128
ACPA positivity, n (%)		15 (75.0)	123 (67.2)	0.172
ACPA titer (U/mL), median [IQR]		121.00 [11.60, 260.35]	74.20 [5.65, 345.75]	0.061
Any comorbidity, n (%)		13 (65.0)	125 (67.9)	0.062
	Respiratory disease, n (%)	3 (15.0)	22 (12.0)	0.089
	Diabetes mellitus, n (%)	5 (25.0)	30 (16.3)	0.216
	Cardiovascular disease, n (%)	2 (10.0)	34 (18.5)	0.244
	Renal disease, n (%)	1 (5.0)	12 (6.5)	0.065
Family history of RA, n (%)		3 (15.0)	40 (21.7)	0.175
Smoking status, n (%)				0.428
	current	2 (10.0)	29 (15.8)	
	former	3 (15.0)	53 (29.0)	
	never	15 (75.0)	101 (55.2)	
Disease Activity Measures				
	PhVAS, median [IQR]	36.50 [28.75, 50.00]	41.00 [30.00, 60.00]	0.313
	PainVAS, median [IQR]	46.50 [30.00, 60.00]	50.00 [30.00, 70.50]	0.219
	PtGA, median [IQR]	50.00 [32.25, 62.00]	50.00 [30.00, 70.00]	0.144

	TJC28, median [IQR]	2.50 [1.00, 5.00]	3.00 [1.00, 5.00]	0.101
	SJC28, median [IQR]	3.00 [1.00, 6.00]	5.00 [2.00, 8.00]	0.418
	ESR, median [IQR]	46.50 [20.00, 62.25]	46.00 [22.50, 72.00]	0.062
	CRP, median [IQR]	1.18 [0.23, 2.05]	1.19 [0.26, 2.91]	0.391
	SDAI, median [IQR]	16.95 [10.82, 23.78]	19.00 [13.65, 27.72]	0.276
	CDAI, median [IQR]	15.45 [8.90, 22.33]	17.00 [12.00, 24.27]	0.216
Radiographic damage				
	mTSS (units), median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 3.00]	0.236
	erosion (units), median [IQR]	0.00 [0.00, 0.50]	0.00 [0.00, 0.50]	0.159
	JSN (units), median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.50]	0.251
Initial treatments (baseline to 24 weeks)				
	MTX, n (%)	14 (70.0)	160 (87.0)	0.422
	bDMARDs, n (%)	1 (5.0)	34 (18.5)	0.428
	TNFi, n (%)	1 (5.0)	9 (12.0)	N/A
	IL-6Ri, n (%)	0 (0.0)	6 (17.6)	N/A
	CTLA4-Ig, n (%)	0 (0.0)	5 (14.7)	N/A
	JAK inhibitor, n (%)	0 (0.0)	1 (2.9)	N/A
	Glucocorticoid, n (%)	5 (25.0)	52 (28.3)	0.074
	Glucocorticoid dose for users (prednisolone equivalent, mg/day)	0.00 [0.00, 0.25]	0.00 [0.00, 1.00]	N/A

Values are shown as median IQR for continuous and n (%) for categorical variables. SMD denotes the absolute standardised mean difference; thresholds of 0.10 (small) and 0.20 (moderate) indicate potentially meaningful imbalance. *p*-values are not presented because inference on baseline differences is not the

objective; this table is intended to describe balance between patients with and without week-24 serum data.

ACPA: anti-citrullinated protein antibody; CDAI: Clinical Disease Activity Index; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; CTLA4-Ig: cytotoxic T-lymphocyte antigen 4-immunoglobulin; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; IL-6Ri: interleukin-6 receptor inhibitor; IQR: interquartile range; JAKi: Janus kinase inhibitor; JSN: joint space narrowing; MTX: methotrexate; mTSS: modified Total Sharp Score; N/A: not applicable; PhVAS: Physician Global Assessment of disease activity (Visual Analogue Scale); PtGA: Patient Global Assessment of disease activity; RA: rheumatoid arthritis; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC28: swollen joint count in 28 joints; SMD: standardised mean difference; TJC28: tender joint count in 28 joints; TNFi: tumour necrosis factor inhibitor

Supplementary Table S6. Adjusted outcomes by cluster: CDAI trajectories and 52-week radiographic progression.

(**A**) Adjusted CDAI by timepoint and between-cluster differences.

Time (weeks)	Adjusted mean CDAI (95% CI)		Between-cluster difference (C2–C1), 95% CI	*p*-value
	Cluster 1	Cluster 2		
0	19.52 [18.49, 20.54]	18.59 [17.39, 19.80]	-0.93 [-2.49, 0.64]	0.247
24	6.34 [5.27, 7.41]	6.80 [5.57, 8.04]	0.46 [-1.17, 2.09]	0.579
52	3.98 [2.88, 5.07]	5.44 [4.16, 6.73]	1.46 [-0.22, 3.14]	0.088

Values are adjusted means (EMMeans) from a linear mixed-effects model, CDAI ~ Time (0/24/52 weeks) × Cluster + age + sex + baseline CDAI + (1 | patient_id). Between-cluster differences (C2–C1) are pairwise marginal mean contrasts at each time point. 95% confidence intervals and two-sided *p*-values are based on the Kenward-Roger small-sample adjustment.

CDAI: Clinical Disease Activity Index; EMMeans: estimated marginal means; CI: confidence interval; C1/C2, Cluster 1/Cluster 2.

(**B**) Adjusted between-cluster differences in structural damage at over 52 weeks (Cluster 2 − Cluster 1)

Time (weeks)	Erosion	JSN
0	-0.10 [-0.72, 0.52]	0.00 [-0.43, 0.43]
24	0.47 [-0.19, 1.12]	-0.03 [-0.48, 0.42]
52	0.61 [-0.06, 1.28]	0.09 [-0.37, 0.55]

Data are presented as β [95% CI], where β is the adjusted mean difference for Cluster 2 minus Cluster 1 at each time point. Estimates derive from linear mixed-effects models with fixed effects for Time (0/24/52 weeks), Cluster, and their interaction (Time×Cluster), adjusted for age, sex, and the corresponding baseline value, with a random intercept for patient. Time-specific contrasts were obtained using emmeans with the Kenward–Roger degrees-of-freedom method.

CI: confidence interval; JSN: joint space narrowing

Supplementary Table S7. Baseline predictors of response to csDMARDs at 24 weeks.

	Group	Responder	Non-Responder	*p*-value
Patient demographics and serology				
Age at diagnosis	Overall	68.0 [56.0, 75.0]	69.0 [58.2–75.8]	0.665
	Cluster 1	69.0 [56.8–77.0]	72.0 [59.0–75.5]	0.756
	Cluster 2	67.0 [52.5–74.0]	63.0 [58.5–75.0]	0.828
RF titer (IU/mL)	Overall	68.5 [22.2–149.5]	55.0 [17.9–145.4]	0.513
	Cluster 1	28.5 [9.5–91.5]	19.2 [6.0–40.3]	0.223
	Cluster 2	129.7 [67.8–227.2]	95.7 [56.0–205.5]	0.430
ACPA titer (U/mL)	Overall	81.1 [6.2–344.9]	62.2 [5.2–415.0]	0.690
	Cluster 1	55.5 [1.3–328.7]	5.1 [1.3–27.5]	0.036*
	Cluster 2	94.4 [32.0–384.0]	233.4 [73.3–482.8]	0.185
Baseline Disease Activity				
TJC28	Overall	2.0 [1.0–4.0]	5.0 [3.0–9.0]	<0.001*
	Cluster 1	2.0 [1.0–4.0]	6.0 [4.5–12.0]	<0.001*
	Cluster 2	2.0 [1.0–4.5]	4.0 [2.0–5.0]	0.202
SJC28	Overall	5.0 [2.0–8.0]	5.0 [3.0–11.0]	0.081
	Cluster 1	4.5 [2.0–7.2]	8.0 [4.0–13.5]	0.010*
	Cluster 2	5.0 [2.0–8.0]	3.0 [2.0–5.5]	0.703
CRP (mg/dL)	Overall	0.9 [0.3–2.6]	2.0 [0.5–5.3]	0.018*
	Cluster 1	0.8 [0.2–2.9]	1.9 [0.3–3.2]	0.328
	Cluster 2	1.1 [0.3–1.9]	2.5 [1.4–6.0]	0.009*
CDAI	Overall	16.3 [11.3–23.0]	22.8 [15.2–32.3]	<0.001*
	Cluster 1	16.1 [11.9–23.0]	27.3 [21.8–36.2]	<0.001*
	Cluster 2	16.9 [11.1–23.1]	20.5 [13.9–23.1]	0.265
Baseline inflammatory mediators				
TNF-α	Overall	5.15 [2.05–10.28]	4.31 [2.45–16.65]	0.921
	Cluster 1	2.16 [1.55–4.38]	2.82 [1.93–4.31]	0.550
	Cluster 2	8.94 [4.34–14.96]	16.15 [4.63–24.55]	0.450
IL-6	Overall	9.91 [3.98–17.84]	16.89 [10.42–33.26]	0.011*
	Cluster 1	5.64 [2.65–14.67]	14.38 [5.14–24.54]	0.058
	Cluster 2	13.50 [7.64–21.25]	23.45 [14.32–49.74]	0.049*
IL-1β	Overall	7.52 [4.10–13.23]	7.57 [2.72–16.18]	0.995
	Cluster 1	3.37 [1.77–5.33]	3.01 [1.77–6.09]	0.976
	Cluster 2	11.81 [8.48–16.79]	14.96 [9.01–27.13]	0.241
IFN-γ	Overall	9.43 [3.03–28.13]	7.11 [2.77–36.95]	0.689
	Cluster 1	2.48 [1.85–5.69]	2.85 [1.57–3.86]	0.853
	Cluster 2	23.15 [10.16–50.60]	39.44 [18.85–72.09]	0.160
IL-23	Overall	18.72 [4.11–61.23]	16.16 [2.38–74.95]	0.810
	Cluster 1	4.16 [2.41–9.27]	2.38 [1.04–7.01]	0.121
	Cluster 2	60.38 [26.80–80.99]	75.10 [51.34–88.62]	0.171

Data are presented as medians [interquartile range] in the original measurement units. *p*-values are from Wilcoxon rank-sum tests comparing Responders *vs*. Non-responders within each stratum (Overall, Cluster 1, Cluster 2). Responders were defined as CDAI remission or low disease activity (REM/LDA) at week 24, and Non-responders as moderate or high disease activity (MDA/HDA). Patients included in this analysis received csDMARD-based treatment without b/tsDMARDs during weeks 0–24. No adjustment for multiple comparisons was applied, and these analyses should be interpreted as exploratory.

ACPA: anti-citrullinated protein antibody; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein;

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IFN-γ: interferon-gamma; IL: interleukin; IQR: interquartile range; NR: Non-responder; R: Responder; RF: rheumatoid factor; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; TNF-α: tumour necrosis factor-alpha.

Supplementary Table S8. Sensitivity analysis: adjusted between-cluster CDAI differences across models.

Time (weeks)	Main model	Sensitivity A	Sensitivity B
0	-0.93 [-2.49, 0.64]	−0.92 [-2.55, 0.71]	−0.88 [-2.44, 0.67]
24	0.46 [-1.17, 2.09]	0.47 [-1.22, 2.17]	0.36 [-1.25, 1.97]
52	1.46 [-0.22, 3.14]	1.54 [-0.21, 3.29]	1.39 [-0.28, 3.05]

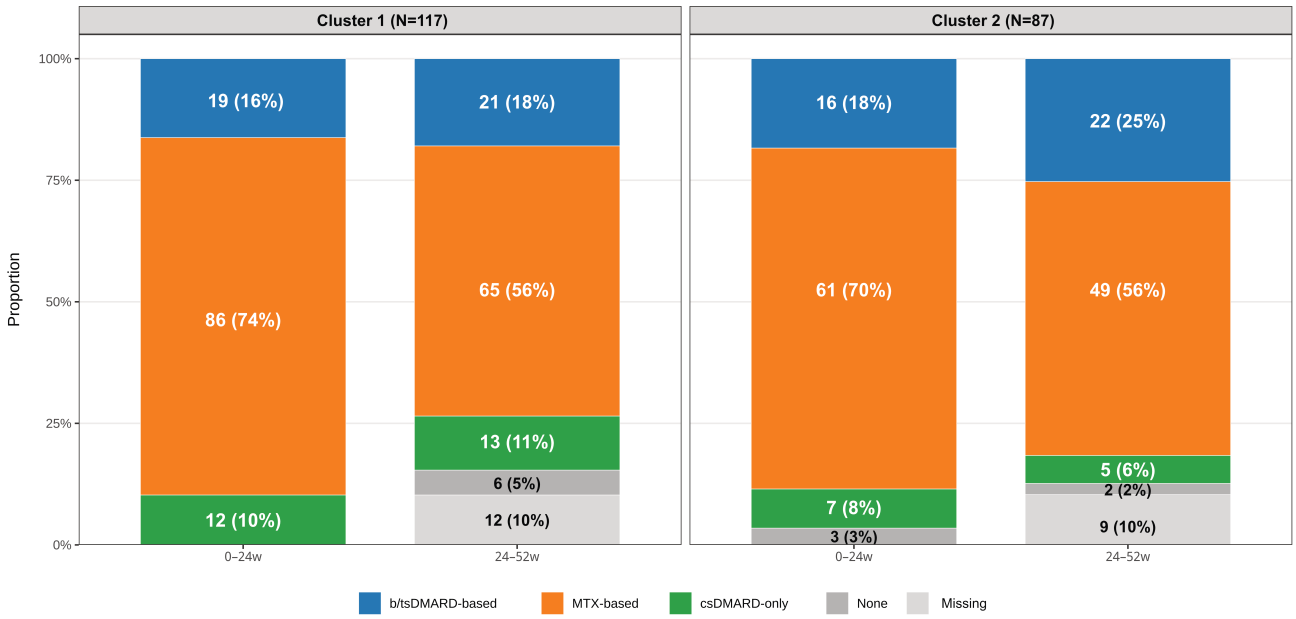
Values are adjusted mean differences in CDAI (Cluster 2 minus Cluster 1) from linear mixed-effects models (random intercept for patient). Main model adjusts for age, sex, baseline CDAI; Sensitivity A adds RF/ACPA positivity and respiratory/renal comorbidity; Sensitivity B further adds time-varying treatment indicators (glucocorticoid use up to the visit; b/tsDMARD use up to the visit). CIs use Kenward-Roger degrees of freedom.

CDAI: Clinical Disease Activity Index; CI: confidence interval; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; b/tsDMARDs: biologic or targeted synthetic disease-modifying anti-rheumatic drugs

Supplementary Table S9. Mapping of k=2 to k=3 cluster assignments.

k=2 / k=3	C1	C2a	C2b	Row Total
C1	117 (100%)	0 (0%)	0 (0%)	117
C2	2 (2.3%)	49 (56.3%)	36 (41.4%)	87
Column total	119	49	36	204

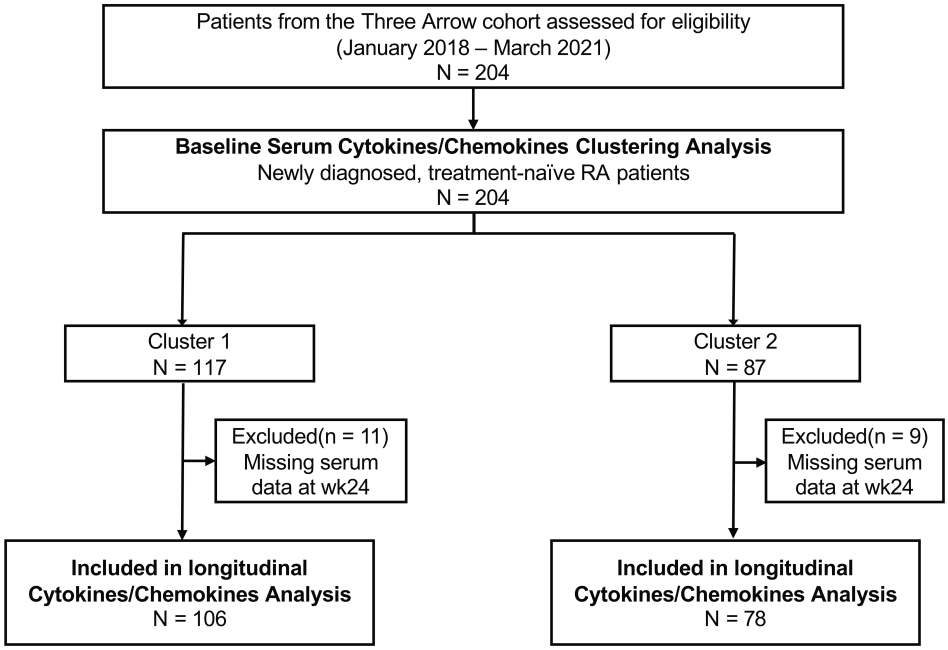
Entries are counts with row percentages in parentheses. When moving from k=2 to k=3, Cluster 1 was fully preserved (purity = 1.00; recall = 1.00), whereas Cluster 2 split into two subclusters (C2a and C2b). Agreement between the k=2 and k=3 assignments was substantial (Adjusted Rand Index, ARI = 0.791).
k: number of clusters; C1/C2a/C2b: cluster labels; ARI: Adjusted Rand Index



Supplementary Fig. S1. Treatment exposure by cluster and period.

Stacked bars show the composition of treatment during 0–24 weeks and 24–52 weeks for Cluster 1 and Cluster 2. Categories are defined as: None (no MTX, no csDMARD, and no b/tsDMARD actually used during the period); MTX-based (any MTX use without b/tsDMARDs, regardless of csDMARD use); csDMARD only (csDMARDs without MTX or b/tsDMARDs); b/tsDMARD-based (any b/tsDMARD use, with or without MTX/csDMARDs). Bar labels shown (percent within cluster×period). Patients without medication information for a period are omitted from the bars and can be reported separately.

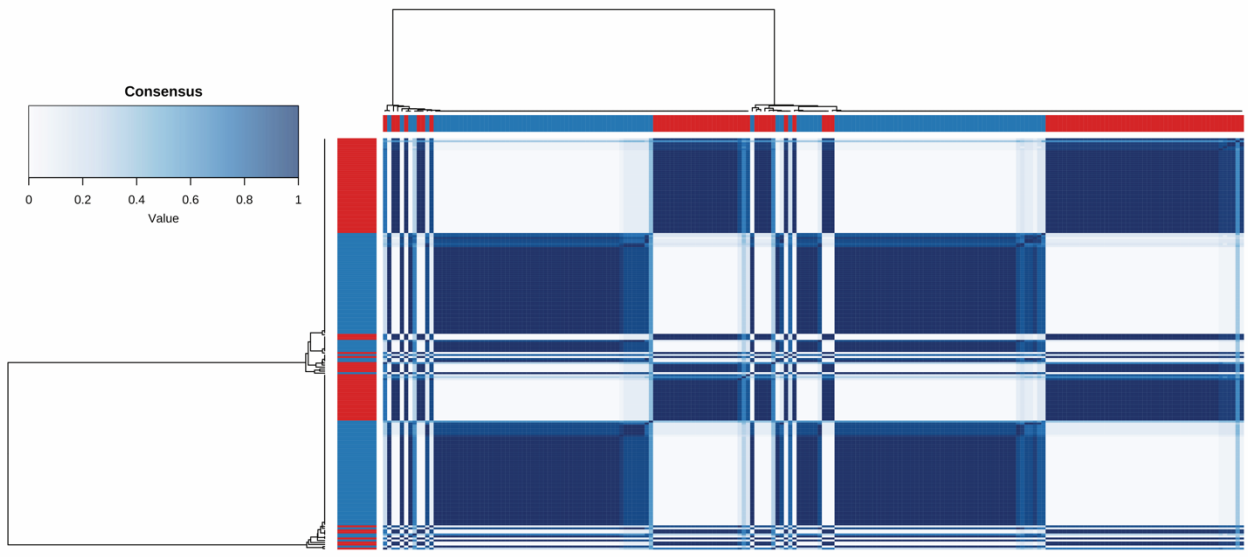
MTX: methotrexate; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; b/tsDMARD: biologic or targeted synthetic DMARD; w: week



Supplementary Fig. 2. Flow diagram of study participants.

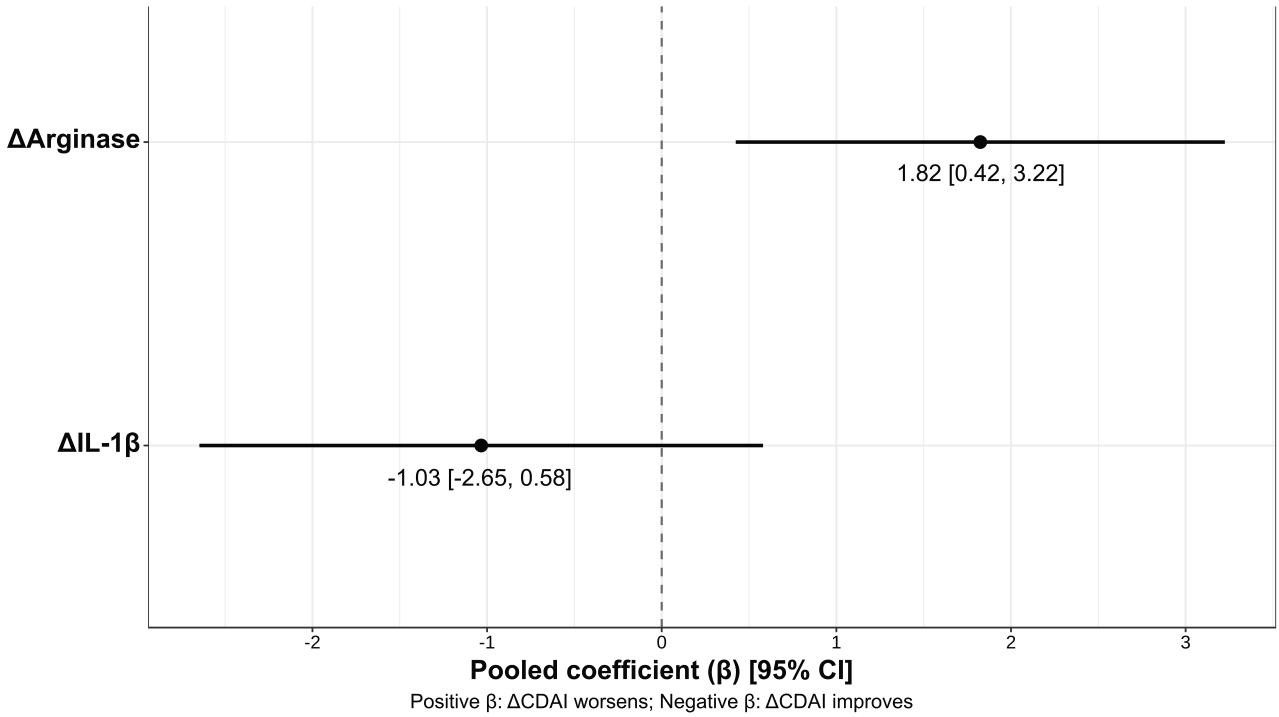
The diagram shows the allocation of 204 DMARDs-naive early rheumatoid arthritis patients into three baseline inflammatory mediator-profile clusters (Cluster 1, n=117; Cluster 2, n=87). It further details their progression to the 24-week longitudinal inflammatory mediator analysis, with numbers included from each cluster (Cluster 1, n=106; Cluster 2, n=78) and reasons for exclusion indicated.

RA: rheumatoid arthritis; wk24: week 24.

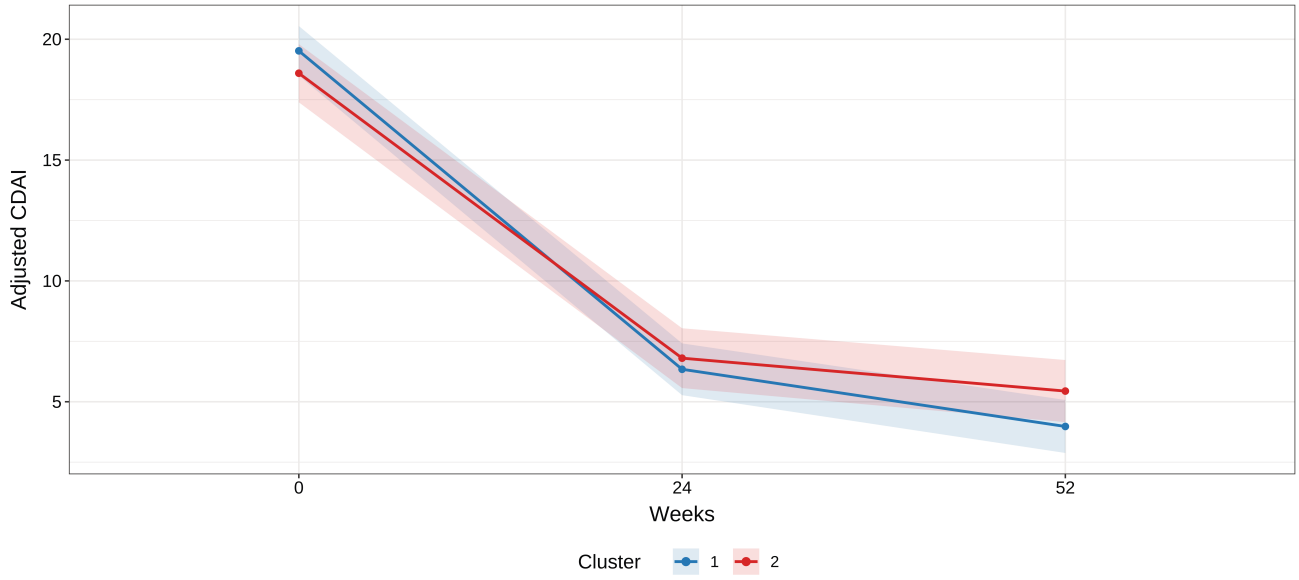


Supplementary Fig. 3. Consensus matrix (k=2).

Each cell shows the proportion (0–1) that two patients were co-assigned to the same cluster across m = 20 imputations. Rows/columns are ordered by Ward.D2 clustering on the 1 − consensus distance; brighter diagonal blocks indicate stable within-cluster co-assignment, and darker off-block regions indicate between-cluster pairs. Side colour bars denote final labels obtained from Ward.D2 on 1 − consensus (Cluster 1, blue; Cluster 2, red). Clustering within each imputation used Euclidean distance and Ward.D2 on baseline markers analysed on the log scale and z-standardised per imputation.

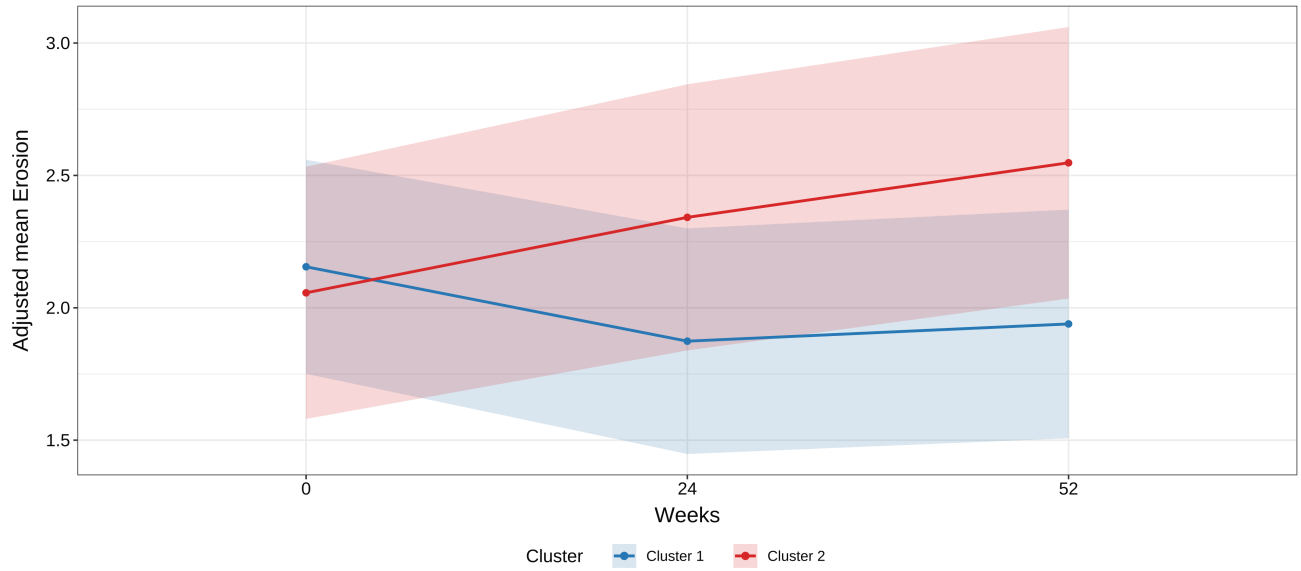


Supplementary Fig. 4. Exploratory analysis of inflammatory mediators associated with ΔCDAI in Cluster 2. No mediators were selected as stable predictors in the primary analysis using the lambda.1se rule. The plot therefore displays selection frequencies from a secondary, exploratory analysis using the more liberal lambda.min rule. Under this relaxed criterion, Arginase-1 (positive association) and IL-1β (negative association) were selected in ≥50% of the 20 imputations. These findings are considered exploratory and should be interpreted with caution.

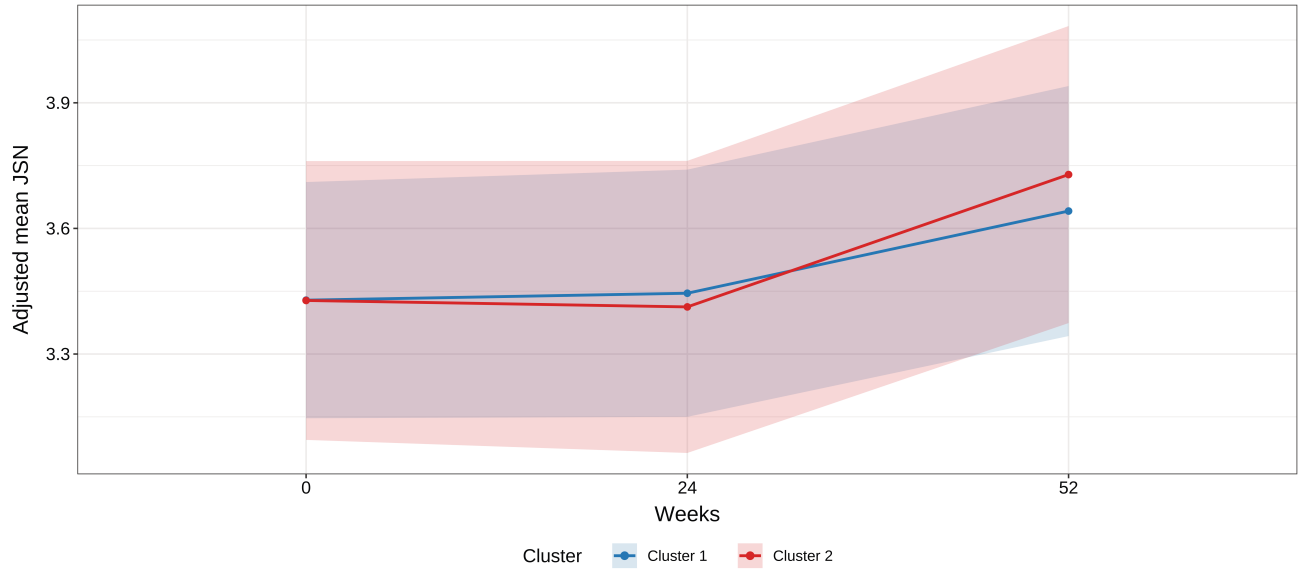


Supplementary Fig. S5. Adjusted CDAI trajectories by cluster at 0, 24, and 52 weeks.
Lines show the adjusted marginal means for CDAI in each cluster; shaded bands indicate 95% confidence intervals. Estimates were obtained from a linear mixed-effects model with a random intercept for patient and fixed effects for Time (0/24/52 weeks), cluster, and their Time×cluster interaction, adjusted for baseline CDAI, age at diagnosis, and sex. Colours denote clusters: Cluster 1 (blue) and Cluster 2 (red).
CDAI: Clinical Disease Activity Index

(A)



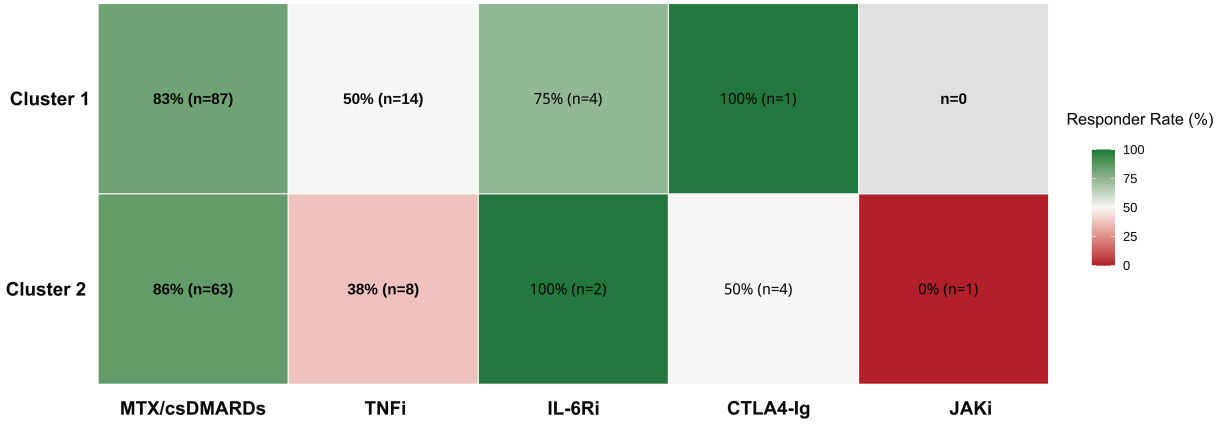
(B)



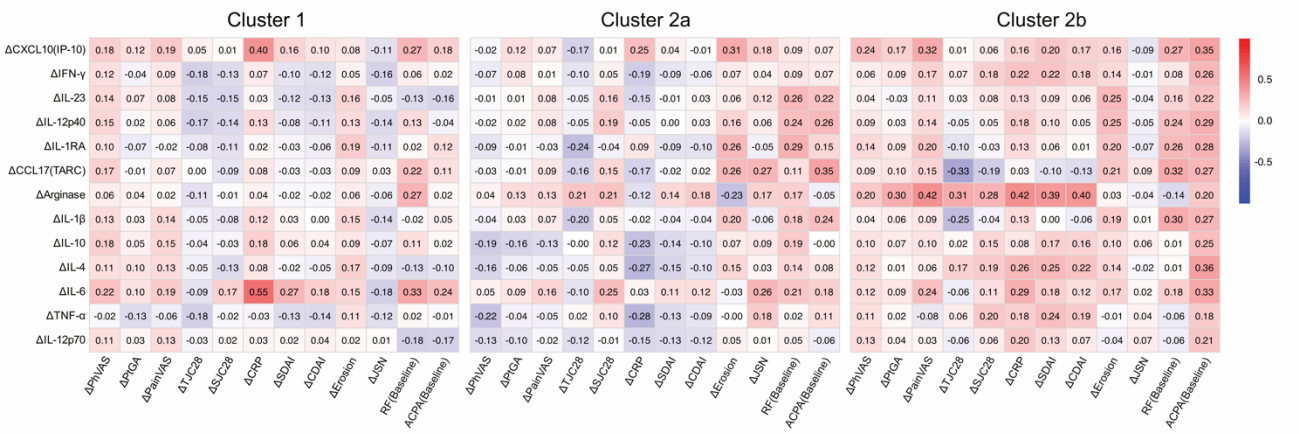
Supplementary Fig. 6. Adjusted structural damage trajectories by cluster at 0, 24, and 52 weeks: (**A**) erosion score; (**B**) joint space narrowing (JSN).

Lines depict adjusted marginal means and shaded bands 95% confidence intervals for structural damage by cluster. Estimates come from linear mixed-effects models with a random intercept for patient and fixed effects for Time (0/24/52 weeks), cluster, and their Time×cluster interaction, adjusted for baseline panel-specific score (erosion or JSN), age at diagnosis, and sex. Colours denote clusters: Cluster 1 (blue) and Cluster 2 (red). (**A**) Erosion. Adjusted marginal mean erosion score by cluster across 0, 24, and 52 weeks. (**B**) JSN. Adjusted marginal mean joint space narrowing (JSN) score by cluster across 0, 24, and 52 weeks.

CI: confidence interval; JSN: joint space narrowing



Supplementary Fig. S7. Treatment response at 24 weeks by cluster and mode of action (MoA).
Heatmap of the CDAI responder rate (%) for each bDMARD mechanism of action (MoA) on the x-axis and cluster on the y-axis. Cell fill uses a diverging scale (red = 0%, white = 50%, green = 100%; limits 0–100%). Gray cells indicate no users (n=0). In-cell labels report the responder rate with the contributing N. MoA exposure is defined over 0–24 weeks.
CDAI: Clinical Disease Activity Index; CTLA4-Ig: cytotoxic T-lymphocyte antigen 4-immunoglobulin; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IL-6Ri: interleukin-6 Receptor inhibitor; JAKi: Janus kinase inhibitor; LDA: low disease activity; MoA: mode of action; MTX: methotrexate; REM: remission; TNFi: tumour necrosis factor inhibitor.



Supplementary Fig. S8. Sensitivity analysis: cluster-specific correlations between 0-24 week changes in serum inflammatory mediators and clinical parameters by 3-Cluster grouping.

Spearman correlation coefficients (ρ) are visualised in heatmaps for the k=3 sensitivity analysis: Cluster C1 (n=119), Cluster C2a (n=49), and Cluster C2b (n=36). The heatmaps depict correlations between 0-24 week changes (Δ) in 13 log-transformed serum inflammatory mediator levels (rows) and 0-24 week changes (Δ) in key clinical parameters (columns). Colour intensity and hue represent the strength and direction of correlations.