Are Cross-sectional Cohorts an Efficient Alternative to Prospective Cohort Design in Real-world Studies?

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Background

- Longitudinal prospective cohort (LPC) study design may be considered the gold standard for real-world studies of change over time in clinical or patient-reported outcomes.
- However, these designs are sometimes non-feasible or cost prohibitive due to long study durations, patient burden, regulatory requirements, and/or logistical/operational complexities.[1,2]
  - Cross-sectional cohort (CSC) design, where subjects are assessed once but the timepoint varies across individuals in terms of their disease journey, may mitigate many of the design challenges posed by LPC's.
  - However, it is unknown how well CSC studies can replicate the outcomes demonstrated in LPC studies.
- Thus, research is needed comparing CSC with LPC study designs.

Objective

- **The objective was to compare CSC study design with LPC study design in a cohort of patients with rheumatoid arthritis (RA).**

Methods

- The study utilized real-world data from 1,716 patients with RA receiving either of two treatments.
- Clinical Disease Activity Index (CDAI) was assessed at 0, 3, 6, 9, and 12 months in the LPC study.
- To simulate the CSC study, a single timepoint was randomly selected as the hypothetical cross-sectional time of assessment.
- Univariate and repeated measures general linear models were used to analyze the data.
  - Between-treatment differences were adjusted in both models for age, gender, duration of disease, prior treatments, and markers of inflammation.

Results

Table 1. Baseline characteristics

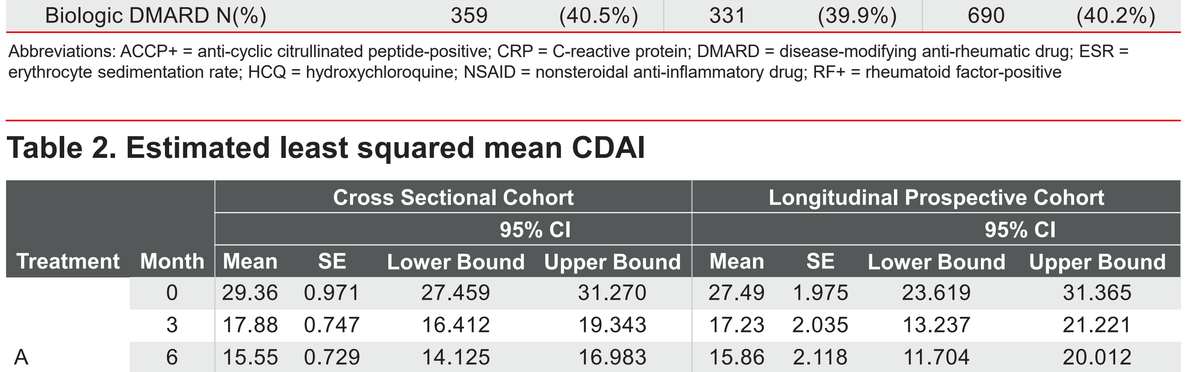
	Treatment					
	A		B		Total	
Age: Mean (SD) years	59.62	(11.46)	60.29	(11.61)	59.94	(11.54)
Gender N(%)						
Female	6,255	73.90%	617	(74.40%)	6872	(83.10%)
Male	231	(26.1%)	213	(25.7%)	444	(25.9%)
Disease Duration Mean (SD) years	7.18	(8.76)	8.02	(9.18)	7.59	(8.97)
CRP Mean (SD) mg/L	2.10	(3.55)	2.01	(3.05)	2.06	(3.32)
ESR Mean (SD) mm/hr	22.38	(17.13)	23.32	(16.63)	22.84	(16.89)
RF+ N(%)	484	(54.6%)	494	(59.5%)	978	(57.0%)
ACCP+ N(%)	284	(32.1%)	280	(33.7%)	564	(32.9%)
Prior Treatments						
Corticosteroids N(%)	211	(23.8%)	185	(22.3%)	396	(23.1%)
NSAIDS N(%)	268	(30.2%)	230	(27.7%)	498	(29.0%)
HCQ N(%)	354	(40.0%)	336	(40.5%)	690	(40.2%)
Sulfasalazine N(%)	142	(16.0%)	140	(16.9%)	282	(16.4%)
Leflunomide N(%)	112	(12.6%)	116	(14.0%)	228	(13.3%)
Gold N(%)	7	(0.8%)	5	(0.6%)	12	(0.7%)
Biologic DMARD N(%)	359	(40.5%)	331	(39.9%)	690	(40.2%)

Abbreviations: ACCP+ = anti-cyclic citrullinated peptide-positive; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; HCQ = hydroxychloroquine; NSAID = nonsteroidal anti-inflammatory drug; RF+ = rheumatoid factor-positive

Table 2. Estimated least squared mean CDAI

		Cross Sectional Cohort				Longitudinal Prospective Cohort			
				95% CI				95% CI	
Treatment	Month	Mean	SE	Lower Bound	Upper Bound	Mean	SE	Lower Bound	Upper Bound
A	0	29.36	0.971	27.459	31.270	27.49	1.975	23.619	31.365
	3	17.88	0.747	16.412	19.343	17.23	2.035	13.237	21.221
	6	15.55	0.729	14.125	16.983	15.86	2.118	11.704	20.012
	9	12.45	0.670	11.131	13.761	13.13	1.700	9.799	16.469
	12	10.52	1.003	8.553	12.488	12.95	1.861	9.297	16.597
B	0	31.10	0.997	29.140	33.051	27.31	1.976	23.437	31.190
	3	15.97	0.730	14.535	17.398	17.76	2.037	13.763	21.754
	6	16.17	0.732	14.735	17.606	15.24	2.120	11.086	19.401
	9	11.85	0.751	10.377	13.324	11.77	1.702	8.435	15.111
	12	12.24	1.039	10.207	14.281	12.15	1.863	8.494	15.800
Total	0	30.23	0.696	28.865	31.595	29.79	0.245	29.309	30.270
	3	16.92	0.522	15.898	17.947	16.20	0.253	15.702	16.695
	6	15.86	0.517	14.848	16.876	15.04	0.263	14.520	15.550
	9	12.15	0.503	11.161	13.135	12.09	0.211	11.679	12.505
	12	11.38	0.722	9.966	12.799	12.06	0.230	11.605	12.509

Figure 1. Estimated least squared mean CDAI



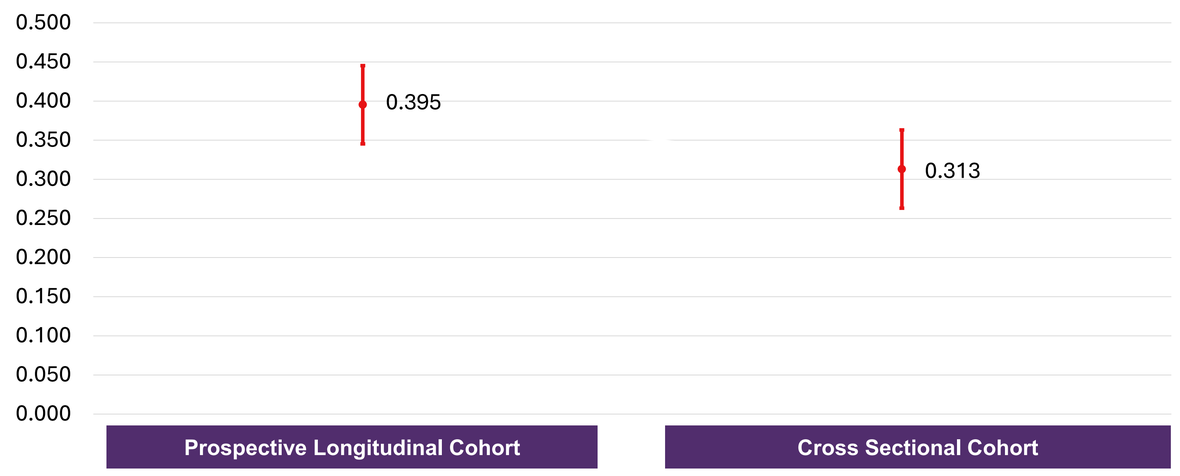
Results (cont.)

Table 3. Covariates

	P-value	
Variable	Cross-sectional Cohort	Longitudinal Prospective Cohort
Treatment	0.559	0.806
Month	0.001	0.001
Treatment * Month	0.136	0.655
Age	0.356	0.501
Gender	0.006	0.025
Disease Duration	0.051	0.025
Baseline CRP	0.061	0.003
Baseline ESR	0.764	0.734
RF	0.000	0.000
ACCP	0.055	0.001
Prior Treatments		
MTX	0.000	0.000
Corticosteroids	0.591	0.477
NSAIDS	0.001	0.000
HCQ	0.008	0.079
Sulfasalazine	0.451	0.040
Leflunomide	0.935	0.161
Gold	0.281	0.957
Biologic	0.000	0.000

Abbreviations: ACCP+ = anti-cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HCQ = hydroxychloroquine; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; RF = rheumatoid factor

Figure 2. Between-group differences



Discussion

- The results of this study showed that the CSC analysis (using general linear models) emulated the results of an LPC analysis (using a repeated measures mixed effects model).
  - Between-group differences with the two analyses were similar.
  - The two methods showed comparable statistical significance for most covariates included in the models.

Limitations

- CSC was simulated from a longitudinal study by selecting random visit numbers at different disease intervals.
- Because timing of assessment in real-world studies may be due to multiple known and unknown factors (i.e., may not be random), assessments of differential attrition and visit patterns would be required to ensure that the CSC model can be used. Adjustments for informed censoring may be necessary.
- This study was based on RA, a progressive chronic condition, where disease severity increases with time.
  - Thus, the results may not apply to diseases where severity does not follow a linear trend.
- While the example was derived from RA, it is possible that the results could be generalized to other paradigms where longitudinal assessments of disease are needed.

Conclusions

- **Cross-sectional analyses could be a valid replacement for longitudinal prospective analyses in some instances.**
- **A CSC approach offer advantages over the longitudinal studies with respect to duration and costs.**
- **Careful considerations must be given to potential issues of bias and suitability of the therapeutic area for utilization of the CSC approach.**

References

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Disclosures

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