COVID Monkeys

HRV Analysis

October 27, 2020

Introduction

- ECG analysis of monkeys with COVID
- HRV performed of available signal
- Monkeys all have SARS-CoV2 infection, half were treated with anti-inflammatories
- Monkeys were scored for clinical severity at several visits

HRV Findings

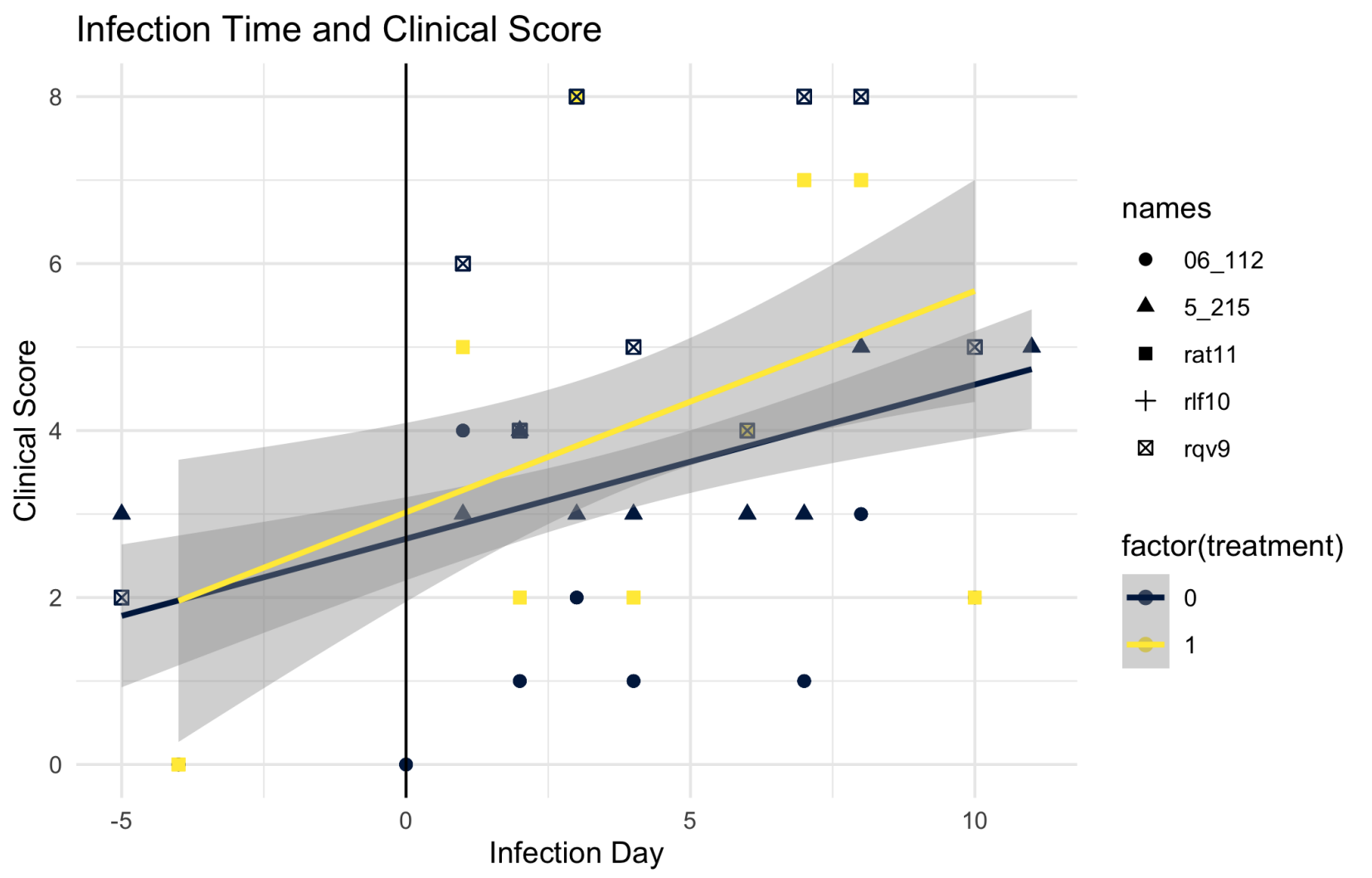
HRV over repeat visits

visit	treatment	n_nmean	sdnn	rmssd	pnn50	hf	lf	ap_en	samp_en	ac	dc
1	0.386	429	14.0	2.24	0.01861	3.63	3.42	0.862	1.52	-2.26	2.066
2	0.487	409	12.7	2.06	0.00805	2.01	3.08	0.926	1.20	-1.15	1.008
3	0.519	439	10.8	1.91	0.00473	2.23	3.27	0.950	1.34	-1.14	0.998
4	0.521	419	17.2	2.24	0.01683	2.75	3.75	0.900	1.29	-1.80	1.644
5	0.515	397	17.3	2.20	0.03783	3.17	4.26	0.898	1.38	-2.07	1.879

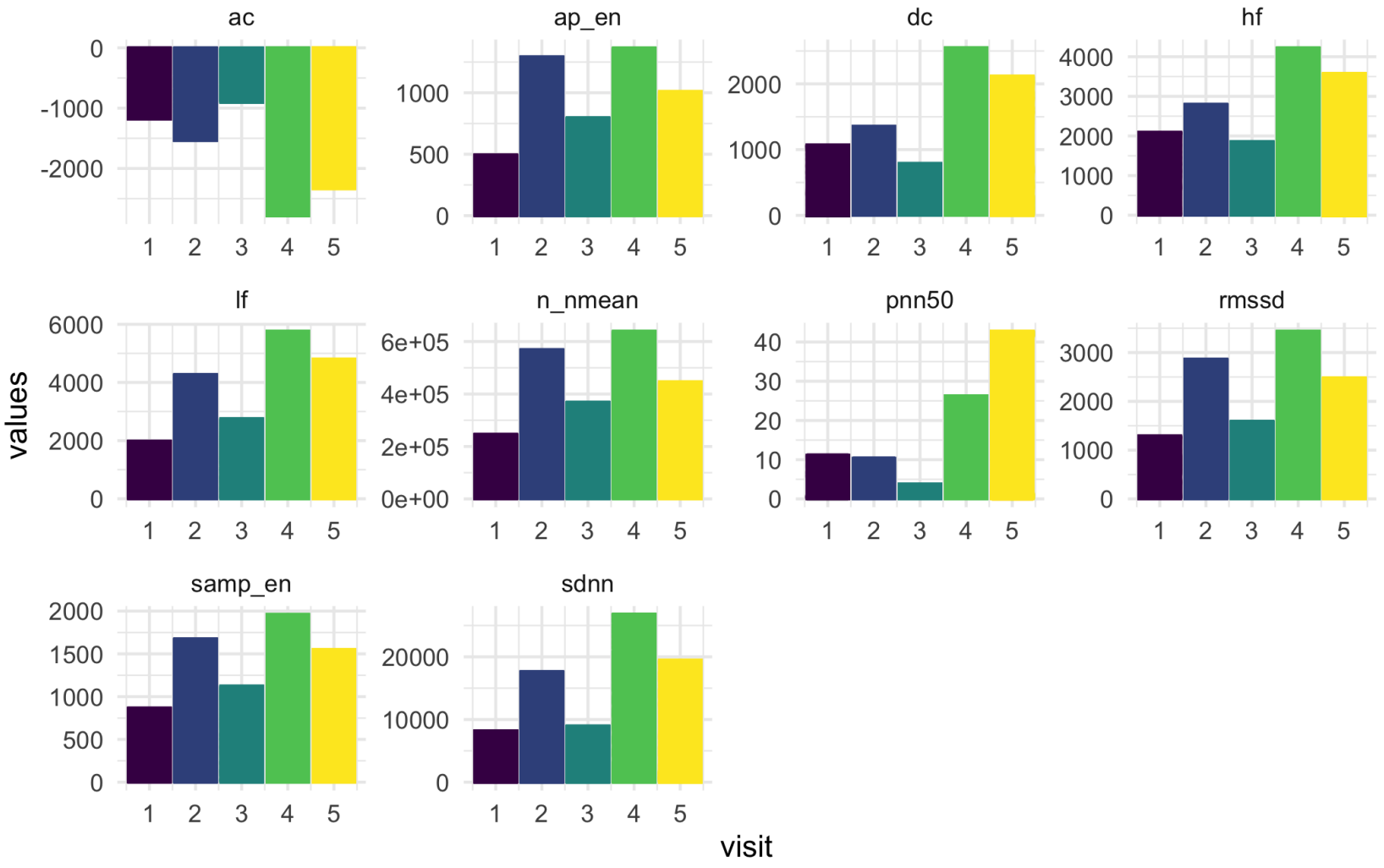
HRV by treatment status

HRV Changes by Treatment Groups										
	HRV Measurements									
Treated	n_nmean	sdnn	rmssd	pnn50	hf	lf	ap_en	samp_en	ac	dc
0										
1	425.6	17.8	2.3	0.0	4.4	4.4	0.8	1.5	−2.7	3.0
2	389.0	16.2	2.3	0.0	2.6	4.0	0.9	1.3	−1.6	1.4
3	383.0	9.1	1.9	0.0	2.6	3.5	1.0	1.4	−1.2	1.0
4	394.6	17.0	2.3	0.0	3.0	3.8	0.9	1.4	−2.0	1.9
5	323.3	5.8	1.8	0.0	1.3	1.9	1.1	1.3	−1.1	0.8
1										
1	434.9	11.8	2.7	0.0	2.8	1.9	1.0	1.2	−1.3	0.6
2	433.6	7.9	1.8	0.0	1.2	2.0	0.9	1.1	−0.6	0.5
3	484.8	11.9	1.8	0.0	1.9	3.2	0.9	1.3	−1.1	0.9
4	427.3	11.6	2.0	0.0	2.1	3.0	1.0	1.2	−1.1	0.9

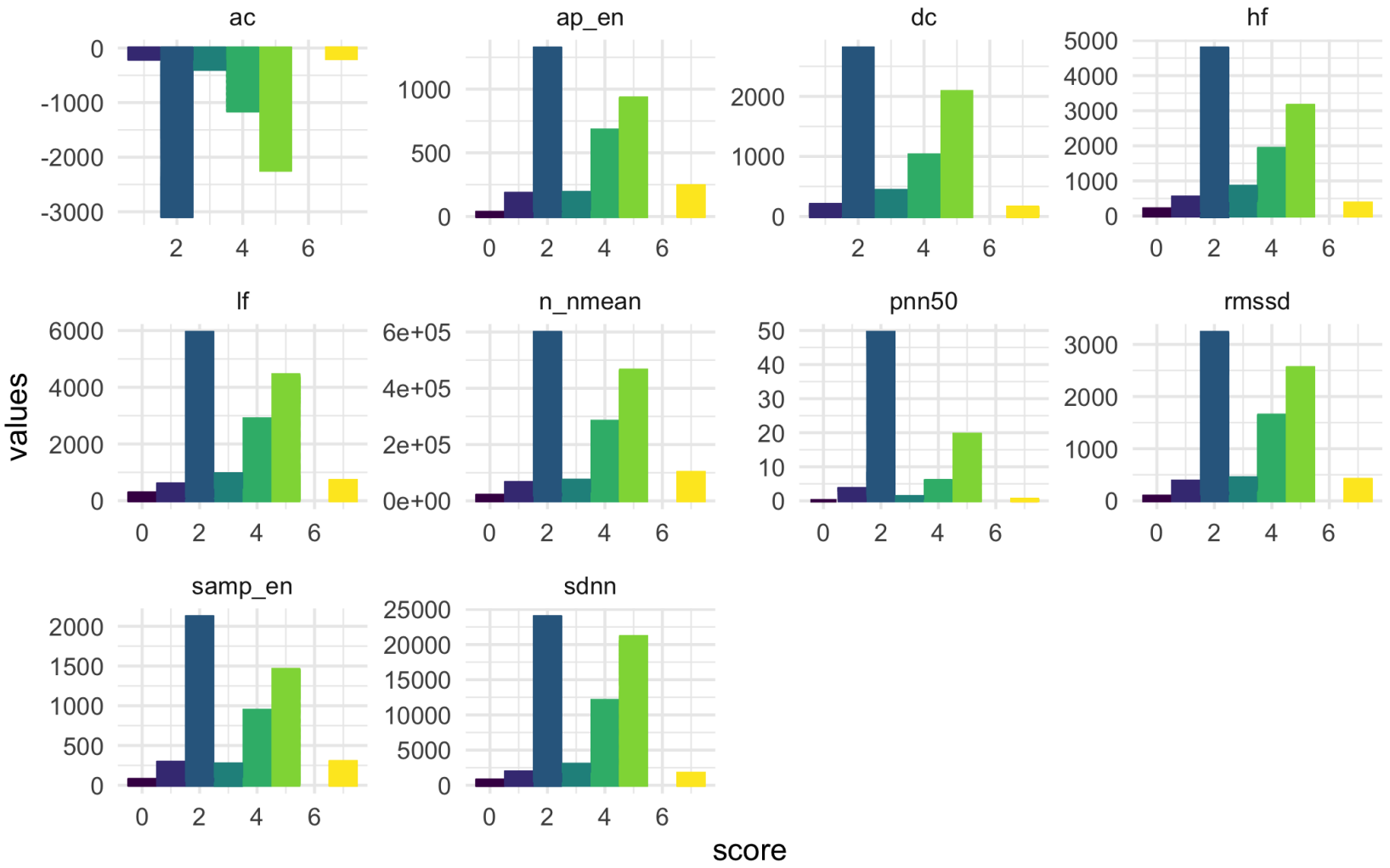
Clinical scores over time



HRV by visit, visualized



HRV by clinical score, visualized



Statistical analysis plan

- linear model of HRV and clinical score at beginning
- linear model of HRV and clinical score at end
- mixed effect models of clinical score by HRV
- mixed model adding on treatment status

Initial Visit

Initial Outcome ~ HRV[1]					
term	estimate	std.error	statistic	conf.low	conf.high
n_nmean	−0.00	0.02	−0.06	−0.07	0.07
sdnn	−0.03	0.28	−0.12	−1.24	1.17
rmssd	0.25	4.03	0.06	−17.07	17.57
pnn50	−13.50	31.19	−0.43	−147.70	120.69
hf	−0.47	2.50	−0.19	−11.24	10.30
lf	−0.06	0.98	−0.06	−4.30	4.18
ap_en	11.92	2.84	4.20	−0.29	24.12
samp_en	3.52	9.80	0.36	−38.63	45.68
ac	−0.82	1.85	−0.44	−8.78	7.15
dc	0.75	1.76	0.43	−6.83	8.33

[1] Linear model with initial, pre-infection clinical severity as the outcome and each initial visit HRV parameter in a separate model as an exposure

Final Visit

Final Outcome ~ HRV[1]						
Linear Models						
term	estimate	std.error	statistic	p.value	conf.low	conf.high
n_nmean	0.01	0.02	0.34	0.77	−0.08	0.10
sdnn	0.19	0.14	1.28	0.33	−0.44	0.81
rmssd	7.41	4.94	1.50	0.27	−13.85	28.67
pnn50	418.39	152.69	2.74	0.11	−238.57	1,075.36
hf	1.06	1.23	0.86	0.48	−4.22	6.33
lf	0.49	1.01	0.49	0.67	−3.84	4.82
ap_en	−5.39	7.29	−0.74	0.54	−36.77	26.00
samp_en	−3.25	10.78	−0.30	0.79	−49.63	43.14
ac	−3.00	1.37	−2.19	0.16	−8.89	2.89
dc	2.40	0.99	2.42	0.14	−1.86	6.66

[1] Linear model with final, post-infection clinical severity as the outcome and each final visit HRV parameter in a separate model as an exposure

Repeat Measures, Unadjusted

Repeat Measures Analysis, Unadjusted[1]					
term	estimate	std.error	statistic	conf.low	conf.high
treatment	−0.32	1.91	−0.17	−4.07	3.43
n_nmean	0.02	0.01	1.79	−0.00	0.05
sdnn	0.18	0.10	1.78	−0.02	0.38
rmssd	−0.48	2.12	−0.23	−4.63	3.68
pnn50	−24.19	23.22	−1.04	−69.71	21.32
hf	1.21	0.92	1.32	−0.59	3.01
lf	1.05	0.61	1.73	−0.14	2.25
ap_en	1.28	3.87	0.33	−6.31	8.88
samp_en	6.24	7.30	0.85	−8.07	20.55
ac	−2.56	0.96	−2.68	−4.44	−0.69
dc	2.24	0.85	2.65	0.58	3.90

[1] Each individual term was tested as an exposure variable independently, with the clinical severity being the outcome. The models were all conditioned on individual monkey and visit to account for repeat measures

Repeat Measures, Adjusted

Repeat Measures by Monkeys and Visit, Adjusted[1]					
term	estimate	std.error	statistic	conf.low	conf.high
treatment	−3.89	2.95	−1.32	−9.68	1.90
n_nmean	0.37	0.11	3.23	0.14	0.59
sdnn	−3.88	1.30	−2.99	−6.42	−1.33
rmssd	−19.41	6.97	−2.79	−33.07	−5.75
pnn50	306.01	86.07	3.56	137.31	474.71
hf	56.26	18.82	2.99	19.37	93.15
lf	−23.62	9.87	−2.39	−42.97	−4.27
ap_en	38.90	12.15	3.20	15.08	62.72

[1] This is a single model comparing the outcome of clinical severity with adjustment for all treatment and HRV parameters. The models were all conditioned on individual monkey and visit to account for repeat measures

Discussion

- In the mixed models (which controlled for repeat measures and individual monkeys), two analyses were performed:
    - Clinical severity by individual parameters (treatment and HRV)
    - Clinical severity with all parameters (treatment and HRV)
- Unadjusted models: Decrease in AC and increase in DC associate with HRV changes over time (repeat visits after infection)
- Adjusted models: HRV happens to show a pattern with repeat visits (not powered to assess AC and DC in these models)