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BACKGROUND

- COVID-19 infection-associated cognitive and olfaction impairments have an unclear pathogenesis, possibly related to systemic disease severity, hypoxia, or illness-associated anxiety and depression. A biomarker for these neurocognitive changes is lacking. The kynurenine pathway (KP) is an interferon stimulated myeloid cell mediated tryptophan degradation pathway important in immune tolerance, neurotoxicity and vascular injury, that is dysregulated in COVID-19. We hypothesized that neurocognitive decline were associated with an activated KP.

METHODS

Study Design & Population

- 128 participants with nasopharyngeal swab-confirmed SARS-CoV-2 infection were enrolled through the Sydney St. Vincent's Hospital COVID-19 ADAPT prospective study. The study is ongoing, and the data for the current analyses were censored on September 15th, 2021; while the first exam was on May 14th, 2020. Blood samples were taken 2-, 4-, 8- and 12-months post diagnosis. Cognition and olfaction were assessed at 2-, 4-, and 12-months post diagnosis: session 1, 2 and 3.
- 127 had concomitant neurocognition and KP data.

COVID-19 disease severity

- Disease severity was assessed with 18 acute symptoms, lung function, and hospitalization status.

Procedures

- Cognition, and olfaction** were assessed with the Cogstate battery and the NIH Toolbox Odor Identification test respectively
- Mental health** was assessed at 2 months with the Depression in the Medically Ill-10 scale, SPHERE 34 Psych subscale and The Impact of Event Scale Revised. Pre-existing psychiatric conditions were recorded.
- KP metabolites** (Log for PIC, QUIN, 3HK, 3HAA, AA, SQRT for KYN, and TRP) were measured by GC-MS and uHPLC.
- Statistical analyses:** The raw cognitive and olfaction data were corrected for age, education, gender, and race/ethnicity. The cognitive follow-up data was corrected for practice effect. Mixed effect regression models with time effect (month post diagnosis, polynomials and random effect selected based on significance and best model fit) tested whether cognition, and olfaction were associated the KP (main and time interaction). Disease severity, mental health and comorbidities were tested as covariates.

COVID-19 is associated with the Kynurenine pathway (KP) activation, and the latter with mild cognitive deficits. The KP may be useful in monitoring and elucidating COVID-19 neuropathogenesis and treatment.

RESULTS

- Study samples' characteristics are presented in Table 1.
- Mild to moderate cognitive and olfaction impairment persisted across the study period (**Fig.1**).
- At 2-month post diagnosis, disease severity was associated with anosmia ($p=.05$), but not cognition; cognitive deficits were more common in those with anosmia ($p=.05$).
- Practice effect corrected cognitive performance declined across the study period (**Fig 2**). This means that in average, participants failed to improved as expected.

Figure 1: Cognitive and olfaction mild impairment per session

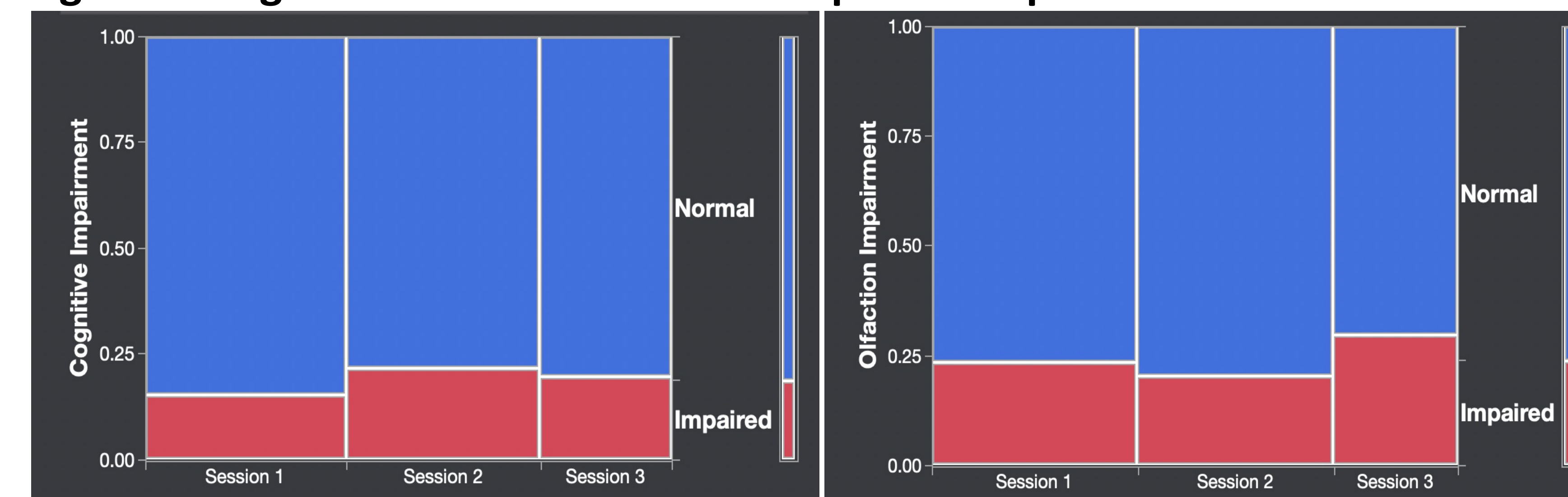
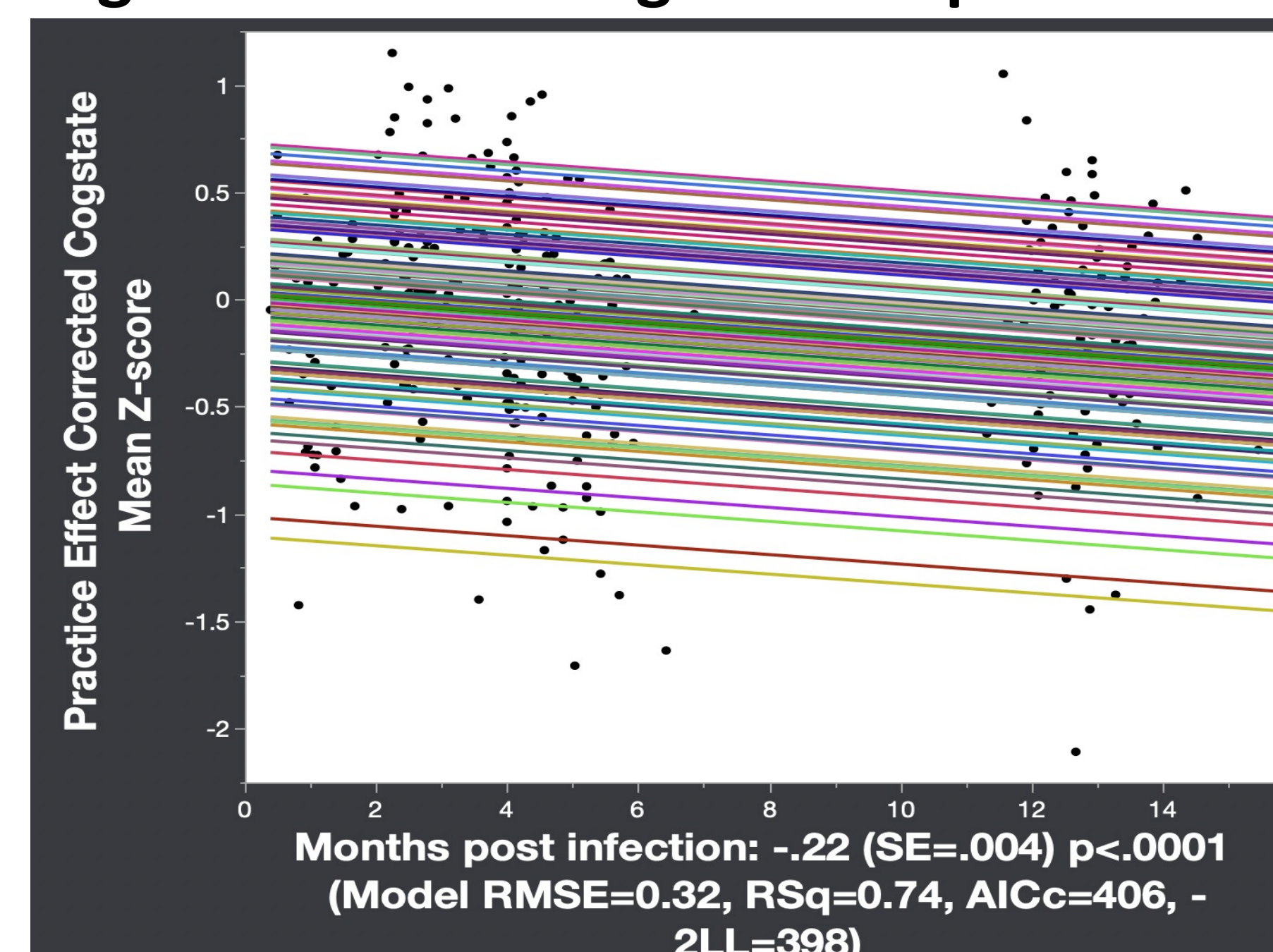


Table 1: Sample's demographic, and clinical characteristics at the 2-month post infection blood test visit (N=128)

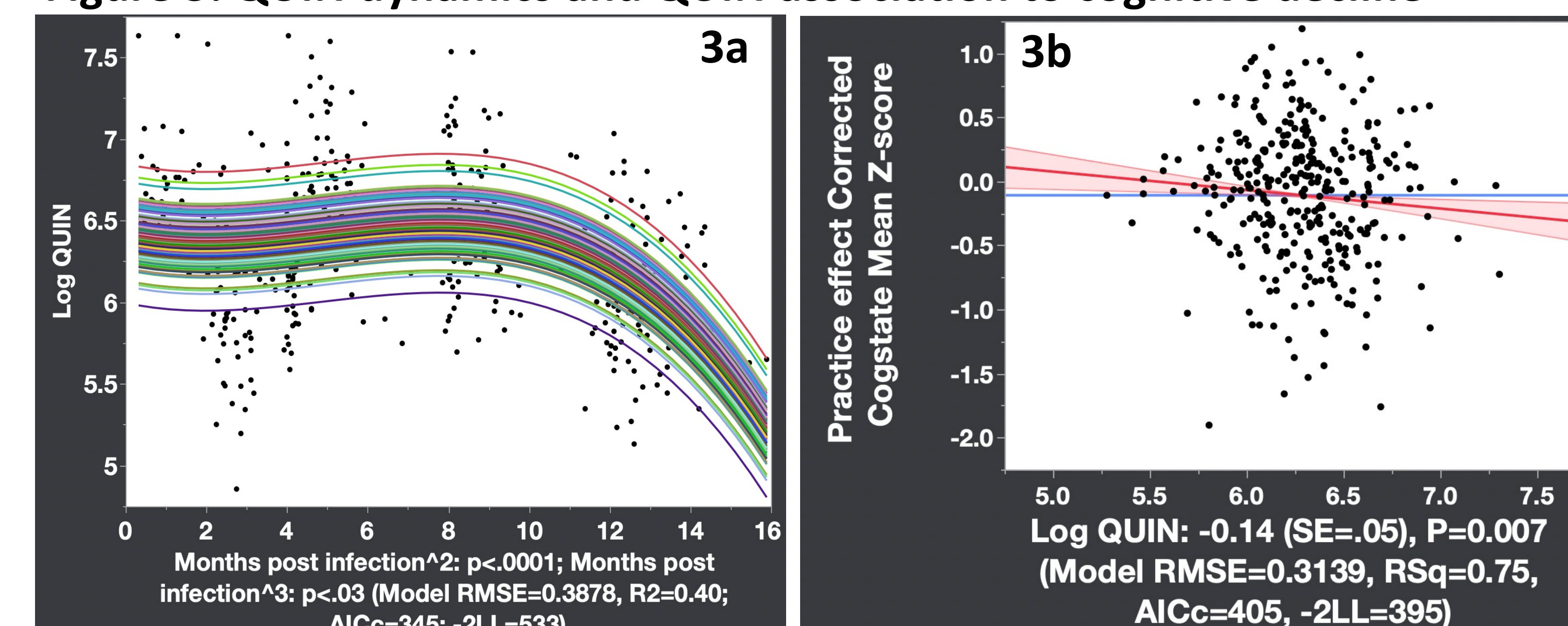
	n	%
Disease severity		
Mild	50	39.0%
Moderate	66	51.6%
Severe	12	9.4%
Sex (Female)	50	42.0%
English-speaking background	121	94.5%
Medical Comorbidities	30	33.6%
Pre-existing Psychiatric Condition	10	8.4%
DMI≥9	34	28.8%
IESR≥33	14	11.8%
SPHERE≥2	46	38.6%
	M	SD
Age (Years)	45.8	14.5
Education (Years)	15.2	2.8
DMI	6.3	6.6
IESR	13.2	14.1
SPHERE	1.8	2.7

Figure 2: Lack of cognitive improvement



- QUIN (**Fig. 3a**) was the most dynamic KP metabolites with both significant quadratic random and fixed effects. 3HK, 3HAA and KYN also increased over time ($p<.001$). Increased QUIN (**Fig. 3b**) associated with poorer longitudinal cognitive performance and independently from comorbidities and disease severity. There was a trend association between greater 2-month post infection anxio-depressive symptoms and cognitive performance ($p=.06$), but this was driven by 5 cases. 2-month post infection anxio-depressive symptoms was elevated as function of increased QUIN ($p<.005$).

Figure 3: QUIN dynamics and QUIN association to cognitive decline



3b: QUIN increased and then steeply decline across the study period and there was a significant difference across patients at baseline as well as across time. Blood KP measurement started 2 months post infection, but the KP increase probably started prior to this measurement. **3a:** Best model for QUIN and longitudinal cognitive performance association was linear and without an interaction term.

CONCLUSIONS

In this cohort composed of mostly mild and moderate COVID-19:

- The KP is activated 8 to 12-month post diagnosis. QUIN has the most dynamic profile and is associated with lower longitudinal cognitive performance, although most patients performs only mildly below demographically corrected norms.
- The KP is not associated with olfaction but is associated with anxio-depressive symptoms; although the current analysis only include mental health symptoms at 2-month post diagnosis.
- The association between QUIN and cognition is independent of comorbidities and disease severity.

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We thank participants for their time and contribution.

The study protocol was approved by St. Vincent's Hospital Human Research Ethics Committee (Reference #2020/ETH00964) and all participants signed an informed consent form.